Induced Fit Docking

Schrödinger Suite 2006

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Contents

Document Conventions

In addition to the use of italics for names of documents, the font conventions that are used in this document are summarized in the table below.

Table 1.1.

Font	Example	Use
Sans serif	Project Table	Names of GUI features, such as panels, menus, menu items, buttons, and labels
Monospace	`$SCHRODINGER/maestro`	File names, directory names, commands, environment variables, and screen output
Italic	*filename*	Text that the user must replace with a value
Sans serif uppercase	CTRL+H	Keyboard keys

In descriptions of command syntax, the following UNIX conventions are used: braces `{ }` enclose a choice of required items, square brackets `[ ]` enclose optional items, and the bar symbol | separates items in a list from which one item must be chosen. Lines of command syntax that wrap should be interpreted as a single command.

In this document, to *type* text means to type the required text in the specified location, and to *enter* text means to type the required text, then press the ENTER key.

References to literature sources are given in square brackets, like this: [10].

Introduction

This document provides information about the Schrödinger Induced Fit Docking (IFD) protocol, which uses Glide™ and Prime™ to induce adjustments in receptor structures, and the Python script that has been developed to automate the process.

Following this introduction, succeeding chapters provide:

- An introduction to Maestro™, the graphical interface for Schrödinger programs, in Chapter 2.
- An Induced Fit Docking tutorial in Chapter 3.
- A description of structure preparation tasks and the Induced Fit Docking panel in Chapter 5.
- Information on using the IFD protocol from the command line in Chapter 6.
- Other documentation and resources for getting help in Chapter 7.

For the most up-to-date information, including answers to frequently asked questions (FAQs) and release announcements, check our web site, http://www.schrodinger.com.

1.1 Induced Fit Docking Applications

In standard virtual docking studies, ligands are docked into the binding site of a receptor where the receptor is held rigid and the ligand is free to move. However, the assumption of a rigid receptor can give misleading results, since in reality many proteins undergo side-chain or backbone movements, or both, upon ligand binding. These changes allow the receptor to alter its binding site so that it more closely conforms to the shape and binding mode of the ligand. This is often referred to as “induced fit” and is one of the main complicating factors in structure-based drug design.

The ability to model induced-fit docking has two main applications:

- Generation of an accurate complex structure for a ligand known to be active but that cannot be docked in an existing (rigid) structure of the receptor.
- Rescue of false negatives (poorly scored true binders) in virtual screening experiments, where instead of screening against a single conformation of the receptor, additional conformations obtained with the induced fit protocol are used.

1.2 The Induced Fit Docking Protocol

Schrödinger has developed and validated an Induced Fit Docking protocol based on Glide and the Refinement module in Prime that accurately predicts ligand binding modes and concomitant structural changes in the receptor.

The Schrödinger IFD protocol models induced fit docking of one or more ligands using the following steps:

1. Constrained minimization of the receptor (Glide protein preparation, refinement only) with an RMSD cutoff of 0.18 Å.
2. Initial Glide docking of each ligand using a softened potential (van der Waals radii scaling). By default, a maximum 20 poses per ligand are retained, and by default poses to be retained must have a Coulomb-vdW score less than 100 and an H-bond score less than –0.05.
3. One round of Prime side-chain prediction for each protein/ligand complex, on residues within a given distance of any ligand pose (default 5 Å).
4. Prime minimization of the same set of residues and the ligand for each protein/ligand complex pose. The receptor structure in each pose now reflects an induced fit to the ligand structure and conformation.
5. Glide redocking of each protein/ligand complex structure within a specified energy of the lowest-energy structure (default 30 kcal/mol). The ligand is now rigorously docked, using default Glide settings, into the induced-fit receptor structure.
6. Estimation of the binding energy (IFDScore) for each output pose.

Schrödinger has developed a Python script that automates the induced fit docking process. This Python script has an interface in Maestro, in which you can specify the structures and enter settings for various options, and then start the job running. The script then completes the protocol without further intervention. The tutorial in Chapter 3 will guide you through the process of entering settings, launching the job, and examining the results.

The structures you use for induced-fit docking must be prepared in the same manner as for Glide. The protein and ligand preparation must precede the use of the protocol outlined above. For details on protein and ligand preparation, see Chapter 4 and Chapter 5 of the *Glide User Manual*, and the *LigPrep User Manual*.

The Induced Fit Docking protocol can also be run from the command line, and you can customize the protocol to perform the Glide and Prime steps of your choice. Chapter 6 describes the input file and how to use it for customization of the protocol.

1.3 Sample Results

In studies of 14 ligand-receptor pairs that required induced fit docking, the Schrödinger Induced Fit Docking protocol yielded an average heavy-atom RMSD of 1.2 Å for the top-ranked output ligand pose to the native ligand. In contrast, rigid-receptor docking with the same ligand-receptor pairs yielded eight cases in which a pose could not be found and an average RMSD of 6.1 Å for the remaining six pairs. Targets included aldose reductase, CDK2 (2), estrogen receptor, HIV protease, protein kinase B, PPAR-gamma, LXR-beta, and thymidine kinase.

1.4 Installation

To run the Schrödinger Suite 2006 Induced Fit Docking protocol, you must install Prime 1.5 and Glide 4.0. To use the automated protocol from Maestro, you must also install Maestro 7.5. Python is automatically installed with any of these products. Induced Fit Docking using Glide 4.0 and Prime 1.5 is supported on SGI and Linux platforms. For installation instructions and information on platform support and hardware and software requirements, see the *Installation Guide*.

1.5 Citing Induced Fit Docking in Publications

The use of this protocol should be acknowledged in publications as:

Schrödinger Suite 2006 Induced Fit Docking protocol; Glide version 4.0, Schrödinger, LLC, New York, NY, 2005; Prime version 1.5, Schrödinger, LLC, New York, NY, 2005.

Introduction to Maestro

Maestro is the graphical user interface for all of Schrödinger's products: CombiGlide™, Epik™, Glide™, Impact™, Jaguar™, Liaison™, LigPrep™, MacroModel®, Phase™, Prime™, QikProp™, QSite™, and Strike™. It contains tools for building, displaying, and manipulating chemical structures; for organizing, loading, and storing these structures and associated data; and for setting up, monitoring, and visualizing the results of calculations on these structures. This chapter provides a brief introduction to Maestro and some of its capabilities. For more information on any of the topics in this chapter, see the *Maestro User Manual*.

2.1 General Interface Behavior

Most Maestro panels are amodal: more than one panel can be open at a time, and a panel need not be closed for an action to be carried out. Each Maestro panel has a Close button so you can hide the panel from view.

Maestro supports the mouse functions common to many graphical user interfaces. The left button is used for choosing menu items, clicking buttons, and selecting objects by clicking or dragging. This button is also used for resizing and moving panels. The right button displays a shortcut menu. Other common mouse functions are supported, such as using the mouse in combination with the SHIFT or CTRL keys to select a range of items and select or deselect a single item without affecting other items.

In addition, the mouse buttons are used for special functions described later in this chapter. These functions assume that you have a three-button mouse. If you have a two-button mouse, ensure that it is configured for three-button mouse simulation (the middle mouse button is simulated by pressing or holding down both buttons simultaneously).

2.2 Starting Maestro

Before starting Maestro, you must first set the `SCHRODINGER` environment variable to point to the installation directory. To set this variable, enter the following command at a shell prompt:

csh/tcsh: `setenv SCHRODINGER` *installation-directory*

bash/ksh: `export SCHRODINGER=`*installation-directory*

You might also need to set the DISPLAY environment variable, if it is not set automatically when you log in. To determine if you need to set this variable, enter the command:

```
echo $DISPLAY
```

If the response is a blank line, set the variable by entering the following command:

csh/tcsh: `setenv DISPLAY` *display-machine-name*`:0.0`

bash/ksh: `export DISPLAY=`*display-machine-name*`:0.0`

After you set the SCHRODINGER and DISPLAY environment variables, you can start Maestro using the command:

```
$SCHRODINGER/maestro options
```

If you add the $SCHRODINGER directory to your path, you only need to enter the command maestro. Options for this command are given in Section 2.1 of the *Maestro User Manual*.

The directory from which you started Maestro is Maestro's current working directory, and all data files are written to and read from this directory unless otherwise specified (see Section 2.8 on page 27). You can change directories by entering the following command in the command input area (see page 8) of the main window:

```
cd directory-name
```

where *directory-name* is either a full path or a relative path.

2.3 The Maestro Main Window

The Maestro main window is shown in Figure 2.1 on page 7. The main window components are listed below.

The following components are always visible:

- **Title bar**—displays the Maestro version, the project name (if there is one) and the current working directory.
- **Auto-Help**—automatically displays context-sensitive help.
- **Menu bar**—provides access to panels.
- **Workspace**—displays molecular structures and other 3D graphical objects.

The following components can be displayed or hidden by choosing the component from the Display menu. Your choice of which main window components are displayed is persistent between Maestro sessions.

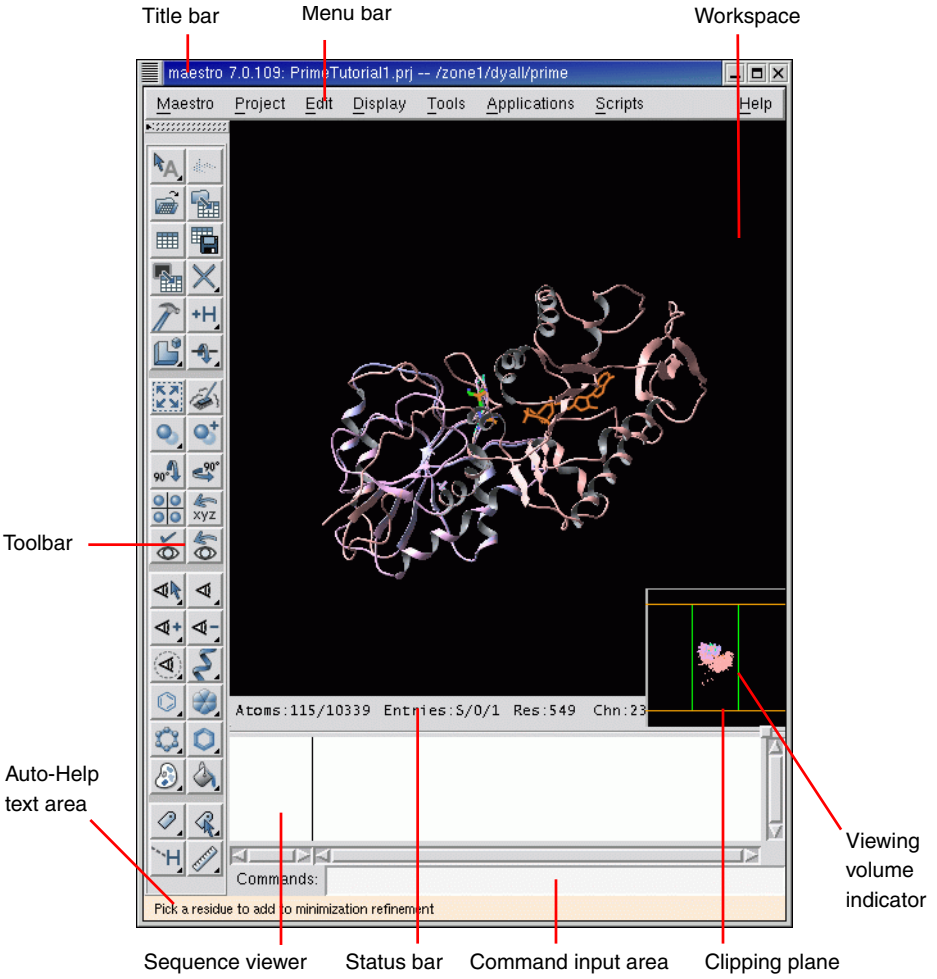

Figure 2.1. The Maestro main window.

- **Toolbar**—contains buttons for many common tasks and provides tools for displaying and manipulating structures, as well as organizing the Workspace.
- **Status bar**—displays information about a particular atom, or about structures in the Workspace, depending on where the pointer pauses (see Section 2.5 of the *Maestro User Manual* for details):
  - **Atom**—displays the chain, residue number, element, PDB atom name, formal charge, and title or entry name (this last field is set by choosing Preferences from the Maestro menu and selecting the Feedback folder).

  - **Workspace**—displays the number of atoms, entries, residues, chains, and molecules in the Workspace.

- **Clipping planes window**—displays a small, top view of the Workspace and shows the clipping planes and viewing volume indicators.
- **Sequence viewer**—shows the sequences for proteins displayed in the Workspace. See Section 2.6 of the *Maestro User Manual* for details.
- **Command input area**—provides a place to enter Maestro commands.

When a distinction between components in the main window and those in other panels is needed, the term *main* is applied to the main window components (e.g., main toolbar).

You can expand the Workspace to occupy the full screen, by pressing CTRL+=. All other components and panels are hidden. To return to the previous display, press CTRL+= again.

2.3.1 The Menu Bar

The menus on the main menu bar provide access to panels, allow you to execute commands, and control the appearance of the Workspace. The main menus are as follows:

- Maestro—save or print images in the Workspace, execute system commands, save or load a panel layout, set preferences, set up Maestro command aliases, and quit Maestro.
- Project—open and close projects, import and export structures, make a snapshot, and annotate a project. These actions can also be performed from the Project Table panel. For more information, see Section 2.4 on page 13.
- Edit—undo actions, build and modify structures, define command scripts and macros, and find atoms in the Workspace.
- Display—control the display of the contents of the Workspace, arrange panels, and display or hide main window components.
- Tools—group atoms; measure, align, and superimpose structures; and view and visualize data.
- Applications—set up, submit, and monitor jobs for Schrödinger's computational programs. Some products have a submenu from which you can choose the task to be performed.
- Scripts—manage and install Python scripts that come with the distribution and scripts that you create yourself. (See Chapter 13 of the *Maestro User Manual* for details.)
- Help—open the Help panel, the PDF documentation index, or information panels; run a demonstration; and display or hide Balloon Help (tooltips).

2.3.2 The Toolbar

The main toolbar contains three kinds of buttons for performing common tasks:

Action—Perform a simple task, like clearing the Workspace.

Display—Open or close a panel or open a dialog box, such as the Project Table panel.

Menu—Display a *button menu*. These buttons have a triangle in the lower right corner.

There are four types of items on button menus, and all four types can be on the same menu (see Figure 2.2):

- **Action**—Perform an action immediately.
- **Display**—Open a panel or dialog box.
- **Object types for selection**—Choose Atoms, Bonds, Residues, Chains, Molecules, or Entries, then click on an atom in the Workspace to perform the action on all the atoms in that structural unit.

  The object type is marked on the menu with a red diamond and the button is indented to indicate the action to be performed.
- **Other setting**—Set a state, choose an attribute, or choose a parameter and click on atoms in the Workspace to display or change that parameter.

The toolbar buttons are described below. Some descriptions refer to features not described in this chapter. See the *Maestro User Manual* for a fuller description of these features.

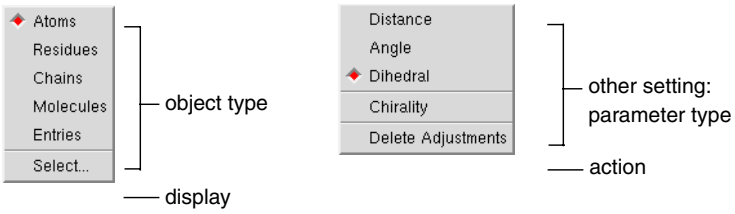

Figure 2.2. The Workspace selection ***button menu and the*** Adjust distances, angles or dihedrals ***button menu.***

Workspace selection
– Choose an object type for selecting
– Open the Atom Selection dialog box

Undo/Redo
Undo or redo the last action. Performs the same function as the Undo item on the Edit menu, and changes to an arrow pointing in the opposite direction when an Undo has been performed, indicating that its next action is Redo.

Open a project
Open the Open Project dialog box.

Import structures
Open the Import panel.

Open/Close Project Table
Open the Project Table panel or close it if it is open.

Save as
Open the Save Project As dialog box, to save the project with a new name.

Create entry from Workspace
Open a dialog box in which you can create an entry in the current project using the contents of the Workspace.

Delete
– Choose an object type for deletion
– Delete hydrogens and waters
– Open the Atom Selection dialog box
– Delete other items associated with the structures in the Workspace
– Click to select atoms to delete
– Double-click to delete all atoms

Open/Close Build panel
Open the Build panel or close it if it is open.

Add hydrogens
– Choose an object type for applying a hydrogen treatment
– Open the Atom Selection dialog box
– Click to select atoms to treat
– Double-click to apply to all atoms

Local transformation
– Choose an object type for transforming
– Click to select atoms to transform
– Open the Advanced Transformations panel

Adjust distances, angles or dihedrals
– Choose a parameter for adjusting
– Delete adjustments

Fit to screen
Scale the displayed structure to fit into the Workspace and reset the center of rotation.

Clear Workspace
Clear all atoms from the Workspace.

Set fog display state
Choose a fog state. Automatic means fog is on when there are more than 40 atoms in the Workspace, otherwise it is off.

Enhance depth cues
Optimize fogging and other depth cues based on what is in the Workspace.

Rotate around X axis by 90 degrees
Rotate the Workspace contents around the X axis by 90 degrees.

Rotate around Y axis by 90 degrees
Rotate the Workspace contents around the Y axis by 90 degrees.

Tile entries
Arrange entries in a rectangular grid in the Workspace.

Reset Workspace
Reset the rotation, translation, and zoom of the Workspace to the default state.

Save view
Save the current view of the Workspace: orientation, location, and zoom.

Restore view
Restore the last saved view of the Workspace: orientation, location, and zoom.

Display only selected atoms
– Choose an object type for displaying
– Click to select atoms to display
– Double-click to display all atoms

Display only
– Choose a predefined atom category
– Open the Atom Selection dialog box

Also display
– Choose a predefined atom category
– Open the Atom Selection dialog box

Undisplay
– Choose a predefined atom category
– Open the Atom Selection dialog box

Display residues within N angstroms of currently displayed atoms
– Choose a radius
– Open a dialog box to set a value

Show, hide, or color ribbons
– Choose to show or hide ribbons
– Choose a color scheme for coloring ribbons

Draw bonds in wire
– Choose an object type for drawing bonds in wire representation
– Open the Atom Selection dialog box
– Click to select atoms for representation
– Double-click to apply to all atoms

Draw atoms in CPK
– Choose an object type for drawing bonds in CPK representation
– Open the Atom Selection dialog box
– Click to select atoms for representation
– Double-click to apply to all atoms

Draw atoms in Ball & Stick
– Choose an object type for drawing bonds in Ball & Stick representation
– Open the Atom Selection dialog box
– Click to select atoms for representation
– Double-click to apply to all atoms

Draw bonds in tube
– Choose an object type for drawing bonds in tube representation
– Open the Atom Selection dialog box
– Click to select atoms for representation
– Double-click to apply to all atoms

Color all atoms by scheme
Choose a predefined color scheme.

Color residue by constant color
– Choose a color for applying to residues
– Click to select residues to color
– Double-click to color all atoms

Label atoms
– Choose a predefined label type
– Delete labels

Label picked atoms
– Choose an object type for labeling atoms
– Open the Atom Selection dialog box
– Open the Atom Labels panel at the Composition folder
– Delete labels
– Click to select atoms to label
– Double-click to label all atoms

Display H-bonds
– Choose bond type:
intra—displays H-bonds within the selected molecule
inter—displays H-bonds between the selected molecule and all other atoms.
– Delete H-bonds
– Click to select molecule

Measure distances, angles or dihedrals
– Choose a parameter for displaying measurements
– Delete measurements
– Click to select atoms for measurement

2.3.3 Mouse Functions in the Workspace

The left mouse button is used for selecting objects. You can either click on a single atom or bond, or you can drag to select multiple objects. The right mouse button opens shortcut menus, which are described in Section 2.7 of the *Maestro User Manual*.

The middle and right mouse buttons can be used on their own and in combination with the SHIFT and CTRL keys to perform common operations, such as rotating, translating, centering, adjusting, and zooming.

Table 2.1. Mapping of Workspace operations to mouse actions.

Mouse Button	Keyboard	Motion	Action
Left		click, drag	Select
Left	SHIFT	click, drag	Toggle the selection
Middle		drag	Rotate about X and Y axes Adjust bond, angle, or dihedral
Middle	SHIFT	drag vertically	Rotate about X axis
Middle	SHIFT	drag horizontally	Rotate about Y axis
Middle	CTRL	drag horizontally	Rotate about Z axis
Middle	SHIFT + CTRL	drag horizontally	Zoom
Right		click	Spot-center on selection
Right		click and hold	Display shortcut menu
Right		drag	Translate in the X-Y plane
Right	SHIFT	drag vertically	Translate along the X axis
Right	SHIFT	drag horizontally	Translate along the Y axis
Right	CTRL	drag horizontally	Translate along the Z axis
Middle & Right		drag horizontally	Zoom

2.3.4 Shortcut Key Combinations

Some frequently used operations have been assigned shortcut key combinations. The shortcuts available in the main window are described in Table 2.2.

Table 2.2. Shortcut keys in the Maestro main window.

Keys	Action	Equivalent Menu Choices
CTRL+B	Open Build panel	Edit > Build
CTRL+C	Create entry	Project > Create Entry From Workspace
CTRL+E	Open Command Script Editor panel	Edit > Command Script Editor
CTRL+F	Open Find Atoms panel	Edit > Find
CTRL+H	Open Help panel	Help > Help
CTRL+I	Open Import panel	Project > Import Structures
CTRL+M	Open Measurements panel	Tools > Measurements
CTRL+N	Create new project	Project > New
CTRL+O	Open project	Project > Open
CTRL+P	Print	Maestro > Print
CTRL+Q	Quit	Maestro > Quit
CTRL+S	Open Sets panel	Tools > Sets
CTRL+T	Open Project Table panel	Project > Show Table
CTRL+W	Close project	Project > Close
CTRL+Z	Undo/Redo last command	Edit > Undo/Redo
CTRL+=	Enter and exit full screen mode (Workspace occupies full screen)	None

2.4 Maestro Projects

All the work you do in Maestro is done within a *project*. A project consists of a set of *entries*, each of which contains one or more chemical structures and their associated data. In any Maestro session, there can be only one Maestro project open. If you do not specify a project when you start Maestro, a *scratch* project is created. You can work in a scratch project without saving it, but you must save it in order to use it in future sessions. When you save or close a project, all the view transformations (rotation, translation, and zoom) are saved with it. When you close a project, a new scratch project is automatically created.

Likewise, if there is no entry displayed in the Workspace, Maestro creates a *scratch* entry. Structures that you build in the Workspace constitute a scratch entry until you save the structures as project entries. The scratch entry is not saved with the project unless you explicitly add it to the project. However, you can use a scratch entry as input for some calculations.

To add a scratch entry to a project, do one of the following:

- Click the Create entry from Workspace button:

- Choose Create Entry from Workspace from the Project menu.
- Press CTRL+C.

In the dialog box, enter a name and a title for the entry. The entry name is used internally to identify the entry and can be modified by Maestro. The title can be set or changed by the user, but is not otherwise modified by Maestro.

Once an entry has been incorporated into the project, its structures and their data are represented by a row in the Project Table. Each row contains the row number, an icon indicating whether the entry is displayed in the Workspace (the In column), the entry title, a button to open the Surfaces panel if the entry has surfaces, the entry name, and any entry properties. The row number is not a property of the entry.

Entries can be collected into groups, and the members of the group can be displayed or hidden. Most additions of multiple entries to the Project Table are done as entry groups.

You can use entries as input for all of the computational programs—Glide, Impact, Jaguar, Liaison, LigPrep, MacroModel, Phase, Prime, QikProp, QSite, and Strike. You can select entries as input for the ePlayer, which displays the selected structures in sequence. You can also duplicate, combine, rename, and sort entries; create properties; import structures as entries; and export structures and properties from entries in various formats.

To open the Project Table panel, do one of the following:

- Click the Open/Close Project Table button on the toolbar

- Choose Show Table from the Project menu
- Press CTRL+T.

The Project Table panel contains a menu bar, a toolbar, and the table itself.

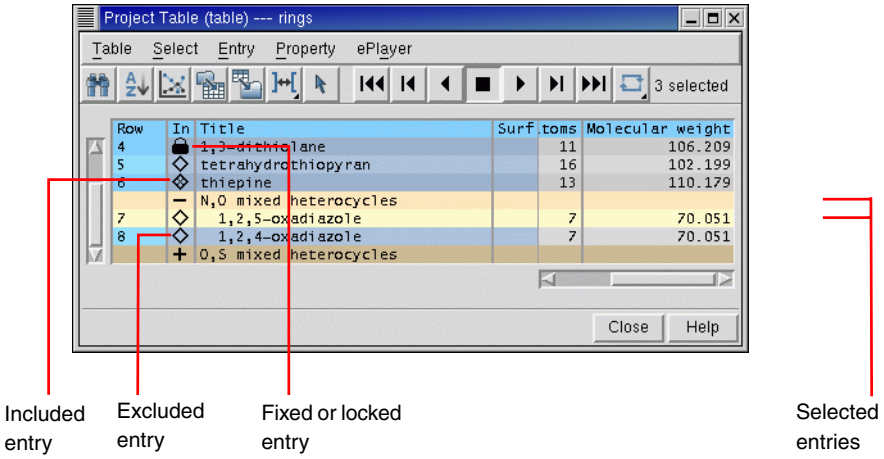

Figure 2.3. The** Project Table **panel.

2.4.1 The Project Table Toolbar

The Project Table toolbar contains two groups of buttons and a status display. The first set of buttons opens various panels that allow you to perform functions on the entries in the Project Table. The second set of buttons controls the ePlayer, which "plays through" the selected structures: each structure is displayed in the Workspace in sequence, at a given time interval. See Section 2.3.2 on page 9 for a description of the types of toolbar buttons. The buttons are described below.

Find
Open the Find panel for locating alphanumeric text in any column of the Project Table, except for the row number.

Sort
Open the Sort panel for sorting entries by up to three properties.

Plot
Open the Plot panel for plotting entry properties.

Import Structure
Open the Import panel for importing structures into the project.

Export Structure
Open the Export panel for exporting structures to a file.

Columns
Choose an option for adjusting the column widths.

Select only
Open the Entry Selection dialog box for selecting entries based on criteria for entry properties.

Go to start
Display the first selected structure.

Previous
Display the previous structure in the list of selected structures.

Play backward
Display the selected structures in sequence, moving toward the first.

Stop
Stop the ePlayer.

Play forward
Display the selected structures in sequence, moving toward the last.

Next
Display the next structure in the list of selected structures.

Go to end
Display the last selected structure.

Loop
Choose an option for repeating the display of the structures. Single Direction displays structures in a single direction, then repeats. Oscillate reverses direction each time the beginning or end of the list is reached.

The status display, to the right of the toolbar buttons, shows the number of selected entries. When you pause the cursor over the status display, the Balloon Help shows the total number of entries, the number shown in the table, the number selected, and the number included in the Workspace.

2.4.2 The Project Table Menus

- Table—find text, sort entries, plot properties, import and export structures, and configure the Project Table.
- Select—select all entries, none, invert your selection, or select classes of entries using the Entry Selection dialog box and the Filter panel.

- Entry—include or exclude entries from the Workspace, display or hide entries in the Project Table, and perform various operations on the selected entries.
- Property—display and manipulate entry properties in the Project Table.
- ePlayer—view entries in succession, stop, reverse, and set the ePlayer options.

2.4.3 Selecting Entries

Many operations in Maestro are performed on the entries selected in the Project Table. The Project Table functions much like any other table: select rows by clicking, shift-clicking, and control-clicking. However, because clicking in an editable cell of a selected row enters edit mode, you should click in the Row column to select entries. See Section 2.4.5 on page 18 for more information on mouse actions in the Project Table. There are shortcuts for selecting classes of entries on the Select menu.

In addition to selecting entries manually, you can select entries that meet a combination of conditions on their properties. Such combinations of conditions are called *filters*. Filters are Entry Selection Language (ESL) expressions and are evaluated at the time they are applied. For example, if you want to set up a Glide job that uses ligands with a low molecular weight (say, less than 300) and that has certain QikProp properties, you can set up a filter and use it to select entries for the job. If you save the filter, you can use it again on a different set of ligands that meet the same selection criteria.

To create a filter:

1. Do one of the following:
   - Choose Only, Add, or Deselect from the Select menu.
   - Click the Entry selection button on the toolbar.

   
2. In the Properties folder, select a property from the property list, then select a condition.
3. Combine this selection with the current filter by clicking Add, Subtract, or Intersect. These buttons perform the Boolean operations OR, AND NOT, and AND on the corresponding ESL expressions.
4. To save the filter for future use click Create Filter, enter a name, and click OK.
5. Click OK to apply the filter immediately.

2.4.4 Including Entries in the Workspace

In addition to selecting entries, you can also use the Project Table to control which entries are displayed in the Workspace. An entry that is displayed in the Workspace is *included* in the Workspace; likewise, an entry that is not displayed is *excluded*. Included entries are marked by an X in the diamond in the In column; excluded entries are marked by an empty diamond. Entry inclusion is completely independent of entry selection.

To include or exclude entries, click, shift-click, or control-click in the In column of the entries, or select entries and choose Include or Exclude from the Entry menu. Inclusion with the mouse works just like selection: when you include an entry by clicking, all other entries are excluded.

It is sometimes useful to keep one entry in the Workspace and include others one by one: for example, a receptor and a set of ligands. You can fix the receptor in the Workspace by selecting it in the Project Table and choosing Fix from the Entry menu or by pressing CTRL+F. A padlock icon replaces the diamond in the In column to denote a *fixed* entry. To remove a fixed entry from the Workspace, you must exclude it explicitly (CTRL+X). It is not affected by the inclusion or exclusion of other entries. Fixing an entry affects only its inclusion; you can still rotate, translate, or modify the structure.

2.4.5 Mouse Functions in the Project Table

The Project Table supports the standard use of shift-click and control-click to select objects. This behavior applies to the selection of entries and the inclusion of entries in the Workspace. You can also drag to resize rows and columns and to move rows.

You can drag a set of non-contiguous entries to reposition them in the Project Table. When you release the mouse button, the entries are placed after the first unselected entry that precedes the entry on which the cursor is resting. For example, if you select entries 2, 4, and 6, and release the mouse button on entry 3, these three entries are placed after entry 1, because entry 1 is the first unselected entry that precedes entry 3. To move entries to the top of the table, drag them above the top of the table; to move entries to the end of the table, drag them below the end of the table.

A summary of mouse functions in the Project Table is provided in Table 2.3.

Table 2.3. Mouse operations in the Project Table.

Task	Mouse Operation
Change a Boolean property value	Click repeatedly in a cell to cycle through the possible values (On, Off, Clear)
Display the Entry menu for an entry	Right-click anywhere in the entry. If the entry is not selected, it becomes the selected entry. If the entry is selected, the action is applied to all selected entries.
Display a version of the Property menu for a property	Right-click in the column header
Edit the text or the value in a table cell	Click in the cell and edit the text or value
Include an entry in the Workspace, exclude all others	Click the In column of the entry
Move selected entries	Drag the entries
Paste text into a table cell	Middle-click
Resize rows or columns	Drag the boundary with the middle mouse button
Select an entry, deselect all others	For an unselected entry, click anywhere in the row except the In column; for a selected entry, click the row number.
Select or include multiple entries	Click the first entry then shift-click the last entry
Toggle the selection or inclusion state	Control-click the entry or the In column

2.4.6 Project Table Shortcut Keys

Some frequently used project operations have been assigned shortcut key combinations. The shortcuts, their functions, and their menu equivalents are listed in Table 2.4.

Table 2.4. Shortcut keys in the Project Table.

Keys	Action	Equivalent Menu Choices
CTRL+A	Select all entries	Select > All
CTRL+F	Fix entry in Workspace	Entry > Fix
CTRL+I	Open Import panel	Table > Import Structures
CTRL+N	Include only selected entries	Entry > Include Only
CTRL+U	Deselect all entries	Select > None
CTRL+X	Exclude selected entries	Entry > Exclude
CTRL+Z	Undo/Redo last command	Edit > Undo/Redo in main window

2.5 Building a Structure

After you start Maestro, the first task is usually to create or import a structure. You can open existing Maestro projects or import structures from other sources to obtain a structure, or you can build your own. To open the Build panel, do one of the following:

- Click the Open/Close Build panel button in the toolbar:

- Choose Build from the Edit menu.
- Press CTRL+B.

The Build panel allows you to create structures by drawing or placing atoms or fragments in the Workspace and connecting them into a larger structure, to adjust atom positions and bond orders, and to change atom properties. This panel contains a toolbar and three folders.

2.5.1 Placing and Connecting Fragments

The Build panel provides several tools for creating structures in the Workspace. You can place and connect fragments, or you can draw a structure freehand.

To place a fragment in the Workspace:

1. Select Place.
2. Choose a fragment library from the Fragments menu.
3. Click a fragment.
4. Click in the Workspace where you want the fragment to be placed.

To connect fragments in the Workspace, do one of the following:

- Place another fragment and connect them using the Connect & Fuse panel, which you open from the Edit menu on the main menu bar or with the Display Connect & Fuse panel on the Build toolbar.

- Replace one or more atoms in the existing fragment with another fragment by selecting a fragment and clicking in the Workspace on the main atom to be replaced.
- Grow another fragment by selecting Grow in the Build panel and clicking the fragment you want to add in the Fragments folder.

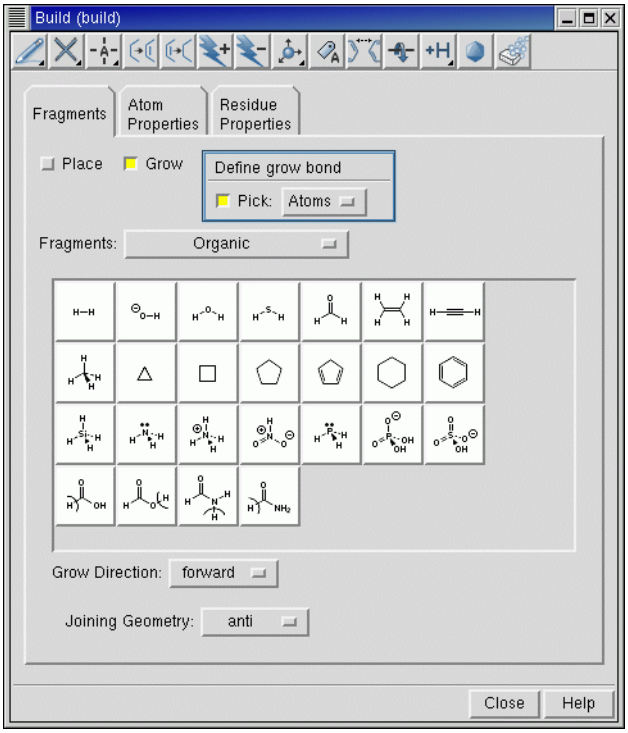

Figure 2.4. The* Build *panel.

Grow mode uses predefined rules to connect a fragment to the *grow bond*. The grow bond is marked by a green arrow. The new fragment replaces the atom at the head of the arrow on the grow bond and all atoms attached to it. To change the grow bond, choose Bonds from the Pick option menu in the Build panel and click on the desired grow bond in the Workspace. The arrow points to the atom nearest to where you clicked.

To draw a structure freehand:

1. Choose an element from the Draw button menu on the Build panel toolbar:

2. Click in the Workspace to place an atom of that element.
3. Click again to place another atom and connect it to the previous atom.
4. Continue this process until you have drawn the structure.
5. Click the active atom again to finish drawing.

2.5.2 Adjusting Properties

In the Atom Properties folder, you can change the properties of the atoms in the Workspace. For each item on the Property option menu—Element, Atom Type (MacroModel), Partial Charge, PDB Atom Name, Grow Name, and Atom Name—there is a set of tools you can use to change the atom properties. For example, the Element tools consist of a periodic table from which you can choose an element and select an atom to change it to an atom of the selected element.

Similarly, the Residue Properties folder provides tools for changing the properties of residues: the Residue Number, the Residue Name, and the Chain Name.

To adjust bond lengths, bond angles, dihedral angles, and chiralities during or after building a structure, use the Adjust distances, angles or dihedrals button on the main toolbar:

You can also open the Adjust panel from this button menu, from the Display Adjust panel button on the Build panel toolbar (which has the same appearance as the above button) or from the Edit menu in the main window.

2.5.3 The Build Panel Toolbar

The toolbar of the Build panel provides quick access to tools for drawing and modifying structures and labeling atoms. See Section 2.3.2 on page 9 for a description of the types of toolbar buttons. The toolbar buttons and their use are described below.

Free-hand drawing
Choose an element for drawing structures freehand in the Workspace (default C). Each click in the Workspace places an atom and connects it to the previous atom.

Delete
Choose an object for deleting. Same as the Delete button on the main toolbar, see page 10.

Set element
Choose an element for changing atoms in the Workspace (default C). Click an atom to change it to the selected element.

Increment bond order
Select a bond to increase its bond order by one, to a maximum of 3.

Decrement bond order
Select a bond to decrease its bond order by one, to a minimum of 0.

Increment formal charge
Select an atom to increase its formal charge by one.

Decrement formal charge
Select an atom to decrease its formal charge by one.

Move
Choose a direction for moving atoms, then click the atom to be moved. Moves in the XY plane are made by clicking the new location. Moves in the Z direction are made in 0.5 Å increments.

Label
Apply heteroatom labels as you build a structure. The label consists of the element name and formal charge, and is applied to atoms other than C and H.

Display Connect & Fuse panel
Open the Connect & Fuse panel so you can connect structures (create bonds between structures) or fuse structures (replace atoms of one structure with those of another).

Display Adjust panel
Open the Adjust panel so you can change bond lengths, bond angles, dihedral angles, or atom chiralities.

Add hydrogens
Choose an atom type for applying the current hydrogen treatment. Same as the Add hydrogens button on the main toolbar, see page 10.

Geometry Symmetrizer
Open the Geometry Symmetrizer panel for symmetrizing the geometry of the structure in the Workspace.

Geometry Cleanup
Clean up the geometry of the structure in the Workspace.

2.6 Selecting Atoms

Maestro has a powerful set of tools for selecting atoms in a structure: toolbar buttons, picking tools in panels, and the Atom Selection dialog box. These tools allow you to select atoms in two ways:

- Select atoms first and apply an action to them
- Choose an action first and then select atoms for that action

2.6.1 Toolbar Buttons

The small triangle in the lower right corner of a toolbar button indicates that the button contains a menu. Many of these buttons allow you to choose an object type for selecting: choose Atoms, Bonds, Residues, Chains, Molecules, or Entries, then click on an atom in the Workspace to perform the action on all the atoms in that structural unit.

For example, to select atoms with the Workspace selection toolbar button:

1. Choose Residues from the Workspace selection button menu:

   

   The button changes to:

   

2. Click on an atom in a residue in the Workspace to select all the atoms in that residue.

2.6.2 Picking Tools

The picking tools are embedded in each panel in which you need to select atoms to apply an operation. The picking tools in a panel can include one or more of the following:

- Pick option menu—Allows you to choose an object type. Depending on the operation to be performed, you can choose Atoms, Bonds, Residues, Chains, Molecules, or Entries, then click on an atom in the Workspace to perform the action on all the atoms in that structural unit.

  The Pick option menu varies from panel to panel, because not all object types are appropriate for a given operation. For example, some panels have only Atoms and Bonds in the Pick option menu.

- All button—Performs the action on all atoms in the Workspace.
- Selection button—Performs the action on any atoms already selected in the Workspace.
- Previous button—Performs the action on the most recent atom selection defined in the Atom Selection dialog box.
- Select button—Opens the Atom Selection dialog box.
- ASL text box—Allows you to type in an ASL expression for selecting atoms.

  ASL stands for Atom Specification Language, and is described in detail in the *Maestro Command Reference Manual*.

- Clear button—Clears the current selection

  

- Show markers option—Marks the selected atoms in the Workspace.

For example, to label atoms with the Label Atoms panel:

1. Choose Atom Labels from the Display menu.
2. In the Composition folder, select Element and Atom Number.
3. In the picking tools section at the top of the panel, you could do one of the following:
   - Click Selection to apply labels to the atoms already selected in the Workspace (from the previous example).
   - Choose Residues from the Pick option menu and click on an atom in a different residue to label all the atoms in that residue.

2.6.3 The Atom Selection Dialog Box

If you wish to select atoms based on more complex criteria, you can use the Atom Selection dialog box. To open this dialog box, choose Select from a button menu or click the Select button in a panel. See Section 5.3 of the *Maestro User Manual* for detailed instructions on how to use the Atom Selection dialog box.

2.7 Scripting in Maestro

Although you can perform nearly all Maestro-supported operations through menus and panels, you can also perform operations using Maestro commands, or compilations of these commands, called *scripts*. Scripts can be used to automate lengthy procedures or repetitive tasks and can be created in several ways. These are summarized below.

2.7.1 Python Scripts

Python is a full-featured scripting language that has been embedded in Maestro to extend its scripting facilities. The Python capabilities within Maestro include access to Maestro functionality for dealing with chemical structures, projects, and Maestro files.

The two main Python commands used in Maestro are:

- `pythonrun`—executes a Python module. (You can also use the alias `pyrun`.) The syntax is:

  `pythonrun` *module*`.`*function*

- `pythonimport`—rereads a Python file so that the next time you use the `pythonrun` command, it uses the updated version of the module. (You can also use the alias `pyimp`.)

From the Maestro Scripts menu you can install, manage, and run Python scripts. For more information on the Scripts menu, see Section 13.1 of the *Maestro User Manual*.

For more information on using Python with Maestro, see *Scripting with Python*.

2.7.2 Command Scripts

All Maestro commands are logged and displayed in the Command Script Editor panel. This means you can create a command script by performing the operations with the GUI controls, copying the logged commands from the Command History list into the Script text area of the panel, then saving the list of copied commands as a script.

To run an existing command script:

1. Open the Command Script Editor panel from the Edit menu in the main window.
2. Click Open Local and navigate to the directory containing the desired script.
3. Select a script in the Files list and click Open.

   The script is loaded into the Script window of the Command Script Editor panel.
4. Click Run Script.

Command scripts cannot be used for Prime operations.

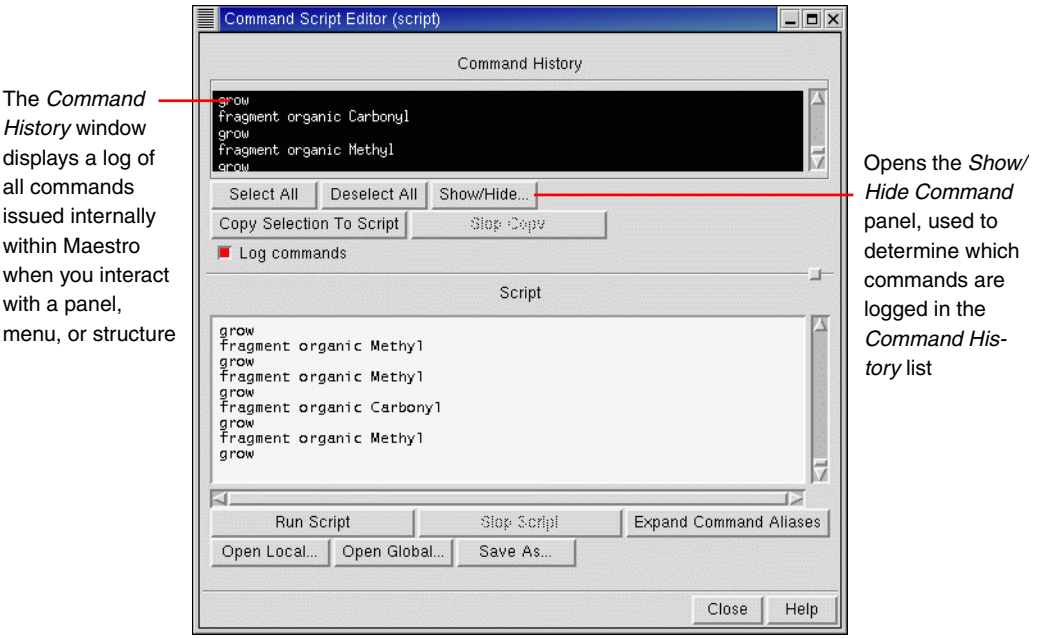

Figure 2.5. The Command Script Editor ***panel.***

2.7.3 Macros

There are two kinds of macros you can create: named macros and macros assigned to function keys F1 through F12.

To create and run a named macro:

1. Open the Macros panel from the Edit menu in the main window.
2. Click New, enter a name for the macro, and click OK.
3. In the Definition text box, type the commands for the macro.
4. Click Update to update the macro definition.
5. To run the macro, enter the following in the command input area in the main window:

   `macrorun` *macro-name*

   If the command input area is not visible, choose Command Input Area from the Display menu.

To create and run a function key macro:

1. Open the Function Key Macros panel from the Edit menu in the main window.
2. From the Macro Key option, select a function key (F1 through F12) to which to assign the macro.
3. In the text box, type the commands for the macro.
4. Click Run to test the macro or click Save to save it.
5. To run the macro from the main window, press the assigned function key.

For more information on macros, see Section 13.5 of the *Maestro User Manual*.

2.8 Specifying a Maestro Working Directory

When you use Maestro to launch Induced Fit Docking jobs, Maestro writes job output to the directory specified in the Directory folder of the Preferences panel. By default, this directory (the file I/O directory) is the directory from which you started Maestro.

To change the Maestro working directory:

1. Open the Preferences panel from the Maestro menu.
2. Click the Directory tab.
3. Select the directory you want to use for reading and writing files.

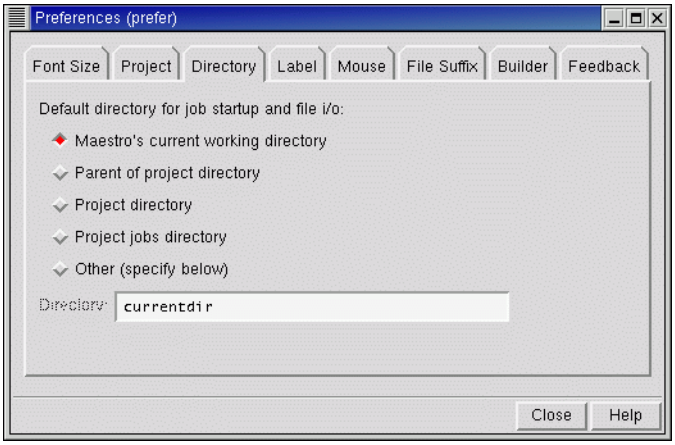

Figure 2.6. T

You can also set other preferences in the Preferences panel. See Section 12.2 of the *Maestro User Manual* for details.

2.9 Undoing an Operation

To undo a single operation, click the Undo button in the toolbar, choose Undo from the Edit menu, or press CTRL+Z. The word Undo in the menu is followed by text that describes the operation to undo. Not all operations can be undone: for example, global rotations and translations are not undoable operations. For such operations you can use the Save view and Restore view buttons in the toolbar, which save and restore a molecular orientation.

2.10 Running and Monitoring Jobs

Maestro has panels for each product for preparing and submitting jobs. To use these panels, choose the appropriate product and task from the Applications menu and its submenus. Set the appropriate options in the panel, then click Start to open the Start dialog box and set options for running the job. For a complete description of the Start dialog box associated with your computational program, see your product's User Manual. When you have finished setting the options, click Start to launch the job and open the Monitor panel.

The Monitor panel is the control panel for monitoring the progress of jobs and for pausing, resuming, or killing jobs. All jobs that belong to your user ID can be displayed in the Monitor panel, whether or not they were started from Maestro. Subjobs are indented under their parent in the job list. The text pane shows various output information from the monitored job, such as the contents of the log file. The Monitor panel opens automatically when you start a job. If it is

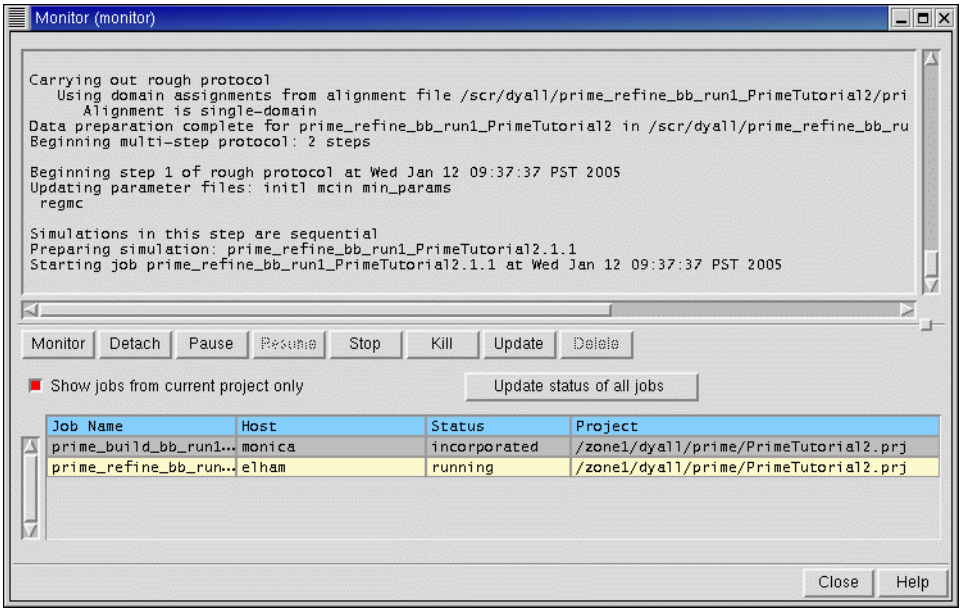

Figure 2.7. The** Monitor **panel.

not open, you can open it by choosing Monitor from the Applications menu in the Maestro main window.

While jobs are running, the Detach, Pause, Resume, Stop, Kill, and Update buttons are active. When there are no jobs currently running, only the Monitor and Delete buttons are active. These buttons act on the selected job. By default, only jobs started from the current project are shown. To show other jobs, deselect Show jobs from current project only.

When a monitored job ends, the results are incorporated into the project according to the settings used to launch the job. If a job that is not currently being monitored ends, you can select it in the Monitor panel and click Monitor to incorporate the results. Monitored jobs are incorporated only if they are part of the current project. You can monitor jobs that are not part of the current project, but their results are not incorporated. To add their results to a project, you must open the project and import the results.

Further information on job control, including configuring your site, monitoring jobs, running jobs, and job incorporation, can be found in the *Job Control Guide* and the *Installation Guide*.

2.11 Getting Help

Maestro comes with automatic, context-sensitive help (Auto-Help), Balloon Help (tooltips), an online help facility, and a user manual. To get help, follow the steps below:

- Check the Auto-Help text box at the bottom of the main window. If help is available for the task you are performing, it is automatically displayed there. It describes what actions are needed to perform the task.
- If your question concerns a GUI element, such as a button or option, there may be Balloon Help for the item. Pause the cursor over the element. If the Balloon Help does not appear, check that Show Balloon Help is selected in the Help menu of the main window. If there is Balloon Help for the element, it appears within a few seconds.
- If you do not find the help you need using either of the steps above, click the Help button in the lower right corner of the appropriate panel. The Help panel is displayed with a relevant help topic.
- For help with a concept or action not associated with a panel, open the Help panel from the Help menu or press CTRL+H.

If you do not find the information you need in the Maestro help system, check the following sources:

- The *Maestro User Manual*
- The Frequently Asked Questions page, found at http://www.schrodinger.com/Support/faq.html

You can also contact Schrödinger by e-mail or phone for help:

- E-mail: help@schrodinger.com
- Phone: (503) 299-1150

2.12 Ending a Maestro Session

To end a Maestro session, choose Quit from the Maestro menu. To save a log file with a record of all operations performed in the current session, click Quit, save log file in the Quit panel. This information can be useful to Schrödinger support staff when responding to any problem you report.

Induced Fit Docking Tutorial

The tutorial in this chapter demonstrates the use of the Schrödinger Induced Fit Docking protocol. Starting with the receptor structure of a protein complexed with a ligand, you will dock a different known active ligand to the active site. The Induced Fit Docking protocol generates multiple poses of the ligand complex, each including unique structural modifications of the receptor to fit the ligand pose, and ranks these poses by GlideScore to find the best structure of the docked complex.

In this case, the protein is human cyclin-dependent kinase 2 (CDK2). The structure of the receptor is derived from the PDB entry 1dm2. The native ligand in the 1dm2 structure is the inhibitor hymenialdisine (HMD); the new ligand that will be docked to that receptor is staurosporine.

This example was chosen as an introduction to the mechanics of using the Induced Fit Docking protocol and is not intended as a research study. The receptor structure provided with the tutorial has been truncated to reduce the time taken by the calculations.

For the purposes of this tutorial, the protein and ligand structures that are provided have already been prepared for Induced Fit Docking. In real applications, you must prepare the protein and the ligands to ensure that they are all-atom structures with correct bond orders and formal charges.

The parameters used in the tutorial have been selected so that the tutorial runs in a relatively short time. In real applications, the default parameters give good results in a very large majority of cases. If you use the default parameters with this tutorial, the Induced Fit Docking job can take approximately 9 CPU hours on a 2 GHz Pentium 4 processor. With the parameters in the tutorial, the total time is about 25 minutes on the same processor.

This tutorial assumes that you have already installed Maestro 7.5, Glide 4.0, Prime 1.5, and supporting third-party programs and databases (PDB, BLAST, HMMER/Pfam) from the Schrödinger CDs. For installation instructions and information on hardware and software requirements, see the *Installation Guide*.

3.1 Preparing for the Tutorial

To prepare for this tutorial, you need to create a working directory, copy files from the Prime distribution to this directory, and start Maestro. The two files that you need, `IFD_ligand.mae` and `IFD_receptor.mae`, are in `$SCHRODINGER/psp-v`*version*`/tutorial`.

1. Change to a directory in which you have write permission.
2. Create a new directory by entering the command:

   ```
   mkdir working-directory
   ```

3. Copy the tutorial files to your working directory:

   ```
   cd working-directory
   cp $SCHRODINGER/psp-vversion/tutorial/IFD* .
   ```

4. Start Maestro by entering the command

   ```
   $SCHRODINGER/maestro &
   ```

3.2 Importing the Receptor

1. Click the Import structures button on the toolbar.

   

2. In the Import panel, select the file `IFD_receptor.mae`.
3. Ensure that the Include in Workspace option selected is First Imported Structure.
4. Click Import.

   The receptor-ligand complex appears in the Workspace, as shown in Figure 3.1. The ligand is a nonstandard residue and is therefore colored differently from the receptor.

5. Close the Import panel.

3.3 Setting Up the Induced Fit Docking Job

- From the Induced Fit Docking submenu of the Applications menu in the main window, choose Induced Fit Docking.

  The Induced Fit Docking panel opens, as shown in Figure 3.2.

3.3.1 Specifying Job Options

In the Job options section, you can enter a job name, select a host, and enter the number of processors to use for the Glide portion and for the Prime portion of the protocol.

1. Change the Job name to `InducedFit1`.
2. Select a host from the Host menu.

   By default, the job is run serially on your local machine. You can distribute the Prime and Glide subjobs over multiple processors. The maximum number of processors you should use is the number of poses, which in this tutorial is 2.
3. If you selected a multiprocessor host, enter 2 in the # Prime CPUs text box and in the # Glide CPUs text box.

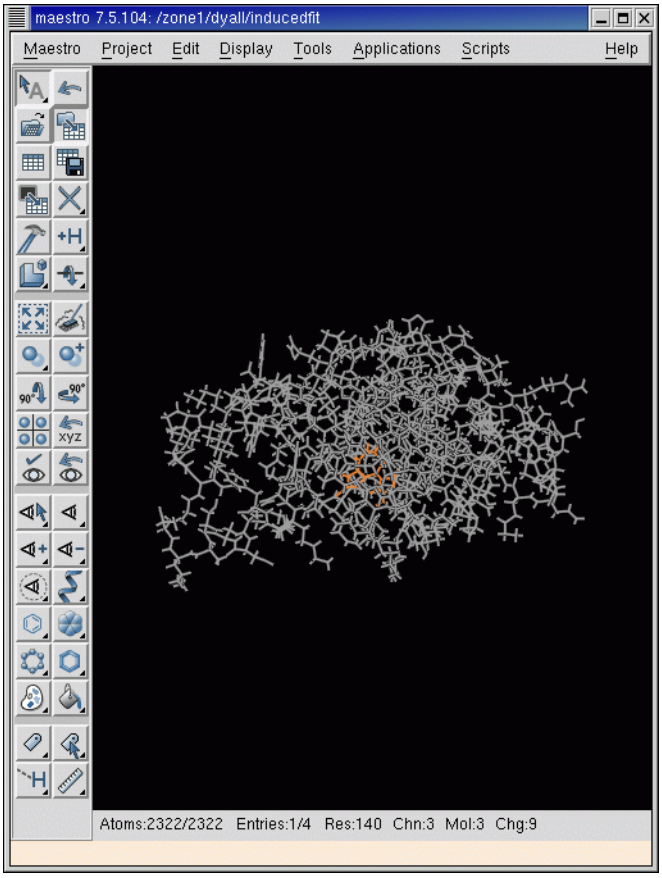

Figure 3.1. The receptor complex in the Workspace

3.3.2 Defining the Receptor and Enclosing Box

The receptor must be distinguished from the complexed ligand in order for the Glide grid generation portion of the protocol to run correctly. The following options are set in the Glide enclosing box section:

1. Ensure that the Center option selected is Centroid of the ligand.
2. Select Pick to the right of the Centroid of the ligand option.
3. Click on a ligand atom in the Workspace.
4. Ensure that the Size option selected is Auto (the default).

   The position and size of the enclosing box are defined automatically, based on the selected ligand.

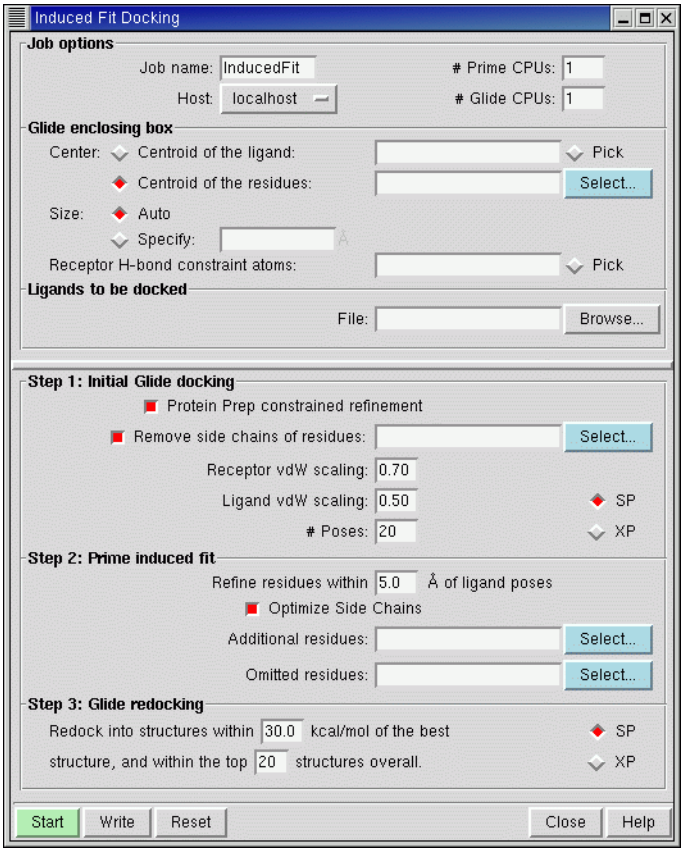

Figure 3.2. The Induced Fit Docking ***panel.***

3.3.3 Specifying a Ligand File To Be Docked

1. In the Ligands to be docked section, click Browse.
2. Open the file containing the ligand, `IFD_ligand.mae`.

3.3.4 Specifying Initial Glide Docking Options

In the Step 1: Initial Glide docking section, you specify the refinement phase of protein preparation, choose whether to temporarily remove active-site residue side chains, and select options for the first round of Glide ligand docking. This preliminary docking is typically performed with both the receptor and the ligand "softened" by van der Waals radii scaling. By default, the scaling factor is 0.50 for the receptor and 0.50 for the ligand.

1. Ensure that Protein Prep constrained refinement is selected (the default).
2. Select the option Remove side chains of residues.

   The Receptor vdW scaling factor is automatically changed to 0.70. Removing side chains from active-site residues provides more room for ligand docking, so the receptor does not need to be quite as soft. The side chains are restored after docking.
3. Click the Select button to the right of the Remove side chains of residues text box.

   The Atom Selection dialog box opens.
4. Click Clear under the ASL text box to clear the previous selection if necessary.
5. In the Residue folder, select Sequence.
6. In the Entry (Chain) list, select IFD_receptor(A).
7. In the Sequence list, select ILE 10 B.
8. Click Add, then click OK.

   Residue 10, isoleucine, is selected for side-chain removal. This residue is temporarily mutated to alanine during the initial Glide docking.
9. Enter 2 in the # Poses text box.

   Normally you would leave this value at the default. This choice is solely to obtain results in a reasonable time.
10. Ensure that the docking precision option selected is SP, standard precision (the default).

3.3.5 Specifying Prime Induced Fit Options

In the section Step 2: Prime induced fit, you will reduce the distance from the ligand that defines residues for refinement. This is done solely to speed up the calculations. In real applications, you should not in general reduce this distance below the default of 5.0 Å.

1. Enter `3.4` in the Refine residues within *m* Å of ligand poses text box.
2. Ensure that Optimize side chains is selected.

The remaining options in this and lower sections are left at their default values. Most of the changed values are for the purpose of shorter execution time. In real applications, you would not make these settings. You are now ready to run the job.

3.4 Running the Induced Fit Docking Job

The Induced Fit Docking protocol is basically a series of Glide and Prime jobs. The panel writes the input file that defines the sequence of jobs, then submits the job for execution.

1. Click Start.

   The message: Job *jobname* launched is displayed in a message box.

2. Click OK to dismiss the message box.

   The following files and directories should be present in your working directory:

```
InducedFit1.inp       InducedFit1_lig.mae   InducedFit1.log
InducedFit1_rec.mae   InducedFit1.restart   InducedFit1_workdir/
```

While the job is running, the job log is written to *jobname*`.log`. The job log lists the input parameters and the ligands to be docked, then reports progress on the job stages of the protocol. The job stages are described in Table 6.1 on page 58. The log also lists the subjobs that the job launches and the output files they produce. You can monitor the progress of the job in the Monitor panel. An example of the log file for this tutorial is shown in Section 6.3 on page 66.

The total time for this job on a 1.8 GHz Pentium 4 processor with 256 kB cache was about 30 minutes.

3.5 Viewing Results

In ordinary flexible-ligand Glide docking, a "pose" or "ligand pose" is a particular conformation of the ligand with respect to the receptor. Because ordinary Glide uses a rigid receptor, each pose combines a unique ligand conformation with an identical receptor structure. In the context of rigid-receptor docking, the term "pose" is equivalent to "ligand pose."

In Induced Fit Docking, both the ligand and the receptor conformation are different for each pose. In the context of induced fit docking, the term "pose" is used for each unique complex structure.

The output structures from the Induced Fit Docking job are stored in a Maestro file, *jobname*`-out.mae`, and in a Maestro project, *jobname*`-results.prj`. Here you will open the Maestro file to examine the results.

1. Click the Import Structures button on the main toolbar.

   

   The Import panel opens.

2. Choose Maestro from the Format menu.
3. Navigate to your working directory and select `InducedFit1-out.mae`.
4. Click Import.

   The first pose from the output file is displayed in the Workspace. By default, only the ligand and the residues that were refined are displayed. If you cannot see the structure, click the Fit to screen button.

   

5. If the Project Table panel is not displayed, click the Open/close project table button on the main toolbar.

   

The input structure, with the native hymenialdisine ligand, and the best staurosporine pose are displayed in Figure 3.3. To display images like these, follow the instructions below.

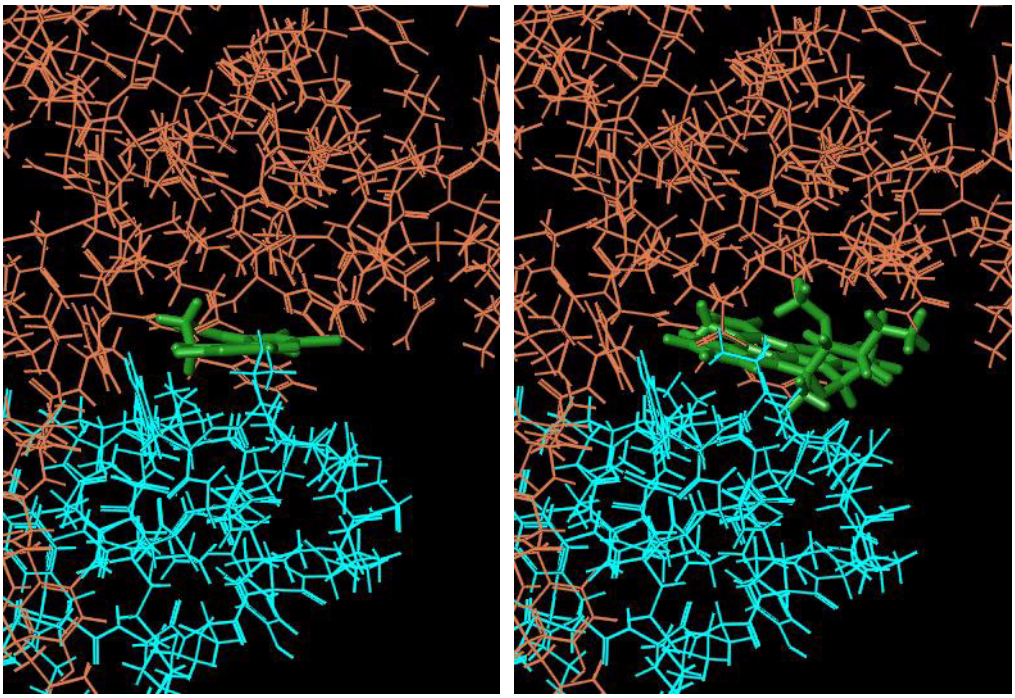

Figure 3.3. The native hymenialdisine structure (left) and the best staurosporine structure (right).

6. Choose All from the Also display button menu.

7. Choose Molecule number from the Color all atoms by scheme button menu.

8. Choose Molecules from the Draw bonds in tube button menu, and click on a ligand atom.

9. Include the receptor structure in the Workspace and repeat Step 6 through Step 8. Do the same for the second pose.
10. Zoom in on the ligand, center it (right-click a ligand atom), and rotate it to a suitable view.

11. Choose Preferences from the Maestro menu.

    The Preferences panel opens.

12. In the Project folder, select Never under Fit to screen when inclusion changes.

    This prevents the view from changing when you include structures successively in the Workspace.

For more information on changing how structures are represented in the Workspace, see Chapter 6 of the *Maestro User Manual*.

Preparing Structures

Before you run an Induced Fit Docking job, you must prepare the receptor and the ligands. Instructions for these preparation tasks are given in the first two sections of this chapter.

4.1 Preparation of the Receptor

Proper preparation of the protein or protein-ligand complex to be used as the receptor is critical to the success of Induced Fit Docking. Both Glide and Prime have certain requirements, and in addition there are requirements for Induced Fit Docking.

In general, the Induced Fit Docking procedure requires a complete, all-atom structure (explicit hydrogens present) with correct bond orders and formal charges. If you are starting with a typical PDB structure (heavy atoms only), the hydrogen atoms are usually implicit, and there may be missing atoms or residues in the structural information, and atom or residue labels that are incorrect. All of these issues must be addressed before proceeding.

When you import a PDB structure into Maestro, it is color coded according to various problems detected in the input data. You can use these color codes to identify and fix the structure. For more information, see Section 3.1.3 of the *Maestro User Manual*. Apart from problems indicated by the color coding, other structural problems may exist that must be fixed. These problems are often only detected by careful inspection of the structure, particularly in the active site. These problems and procedures for fixing them are described below.

When you have fixed the immediate problems, you should perform the first part of the protein preparation required for Glide, as described in Chapter 4 of the *Glide User Manual*. You should stop at Step 5 of the procedure given in Section 4.2 of the *Glide User Manual*. You should not perform the protein preparation in the Protein Preparation panel, as this preparation is done in the Induced Fit Docking procedure.

The general steps in the protein preparation procedure for Induced Fit Docking are:

1. Import the PDB protein structure.
2. Examine the structure for problems, including noting the color code.
3. Fix bond orders, formal charges, and atom names.

   The ligand residues are usually the ones that are colored orange. Fixing the ligand is a prerequisite for any Prime refinement calculation that you may do to fix other problems.

This is not the same as preparation of the ligands for docking, which is treated in the next section.

4. Fix residues that are missing atoms with a Prime side-chain prediction.
5. Check for missing residues.

   The residues at the breaks are not usually color-coded. If there are breaks, you will need to do a Prime calculation to predict the structure of the missing residues.
6. Check the active site for incorrect side-chain geometry, protonation state or tautomerization, and fix as appropriate.
7. Perform the remainder of the Glide protein preparation.
8. Run a Prime Energy calculation to check that all the problems were fixed.

4.1.1 Correcting Bond Orders, Formal Charges and Atom Names

Residues for which Maestro was unable to assign all the bond orders are colored orange. These are usually in the ligand. Residues that have incorrect PDB atom names are colored blue or red. If you need to apply the PDB import color scheme, choose PDB Conversion Status from the Color all atoms by scheme toolbar button menu.

Before you can run Prime, you must fix the bond orders, formal charges, and PDB atom names, which you can do with the procedures given below. All these actions can be done from the Build panel, which you open by clicking the Open/Close Build panel button on the main toolbar.

Prior to manually correcting bond orders, you should use the automatic facility provided with Maestro for this task. To do so, choose Assign Bond Orders from the Tools menu. This script will fix most of the bond orders. Then check the structure for any remaining problems not treated by this tool.

Check also for groups that you expect to have formal charges, to ensure that these charges are correct. Note that the symmetry of nitro and carboxylate groups is automatically accounted for. You should assign the formal charges and bond orders according to the Lewis structure.

Once you have finished with these procedures, check that the ligand is completely fixed.

To assign bond orders (orange residues):

1. Choose Assign Bond Orders from the Tools menu.
2. Inspect the orange residues and any other residues in the ligand for any remaining bond orders that are incorrect.
3. If there are still incorrect bond orders, click the Increment bond order or Decrement bond order button on the Build panel toolbar.

4. Click the bonds in the Workspace structure that needs correction.

To view and change formal charges:

1. From the Label atoms button menu on the main toolbar, choose Formal Charge.

   Charges are displayed for atoms that are charged.
2. Click the Increment formal charge or Decrement formal charge button on the Build panel toolbar.

3. Click on an incorrectly charged atom in the Workspace until its charge is correct.

   The formal charge is incremented or decremented by one unit for each click.

To correct PDB atom names (blue or red residues):

1. From the Label atoms button menu on the main toolbar, choose PDB Atom Name.

2. In the Atom Properties folder, choose PDB Atom Name from the Property option menu.
3. Ensure that Pick is selected in the Apply PDB atom name section, and that Atoms is chosen from the Pick option menu.
4. Zoom in on one of the blue or red residues (middle+right mouse buttons).
5. For each incorrectly-named atom, enter the correct PDB atom name in the PDB atom name text box, then click on the atom.
6. Repeat Step 4 and Step 5 for each incorrect residue.

4.1.2 Adding Missing Atoms

Residues that are colored red are residues for which there is missing density, which means that some atoms are missing. To fix this problem you should use the Prime Refinement panel to do a side-chain prediction, and use the refined structure for Induced Fit Docking. When you come to setting up the Induced Fit Docking job, you should also consider selecting any of these residues that are close to the active site for mutation—see Section 5.4 on page 55.

The Python script `sel_red.py`, which is available from the Script Center on the Schrödinger web site, http://www.schrodinger.com, can be used to select all the red residues. It also creates an atom set containing these residues, so you can use them for later steps, such as selecting side chains for mutation. You can also select the red residues in the Atom Selection dialog box by choosing PDB Conversion Status from the list in the Residues folder.

To refine side chains in a protein receptor with missing atoms (red residues):

1. Fix any bond orders, formal charges, and misnamed atoms in the ligand, and add hydrogens to the ligand.

   The orange residues are usually ligand residues, so fixing the orange residues first will generally address this concern.

2. Double-click the Add hydrogens button in the main window toolbar.

   

   Hydrogen atoms are added to all atoms as needed to complete the valence.

3. Choose Refinement from the Prime submenu of the Applications menu.

   The Refinement panel opens.

4. Choose Predict Side Chains from the Task option menu.

5. In the Residues for side chain refinment section, click Select.

   The Atom Selection dialog box opens.

6. In the Residues folder, choose PDB Conversion Status from the property list.

   The available PDB Conversion Status are displayed in the list in the center.

7. Choose Missing atoms from the PDB Conversion Status list.

8. Click Add, then click OK.

   The Atom Selection dialog box closes. The red residues are now selected for refinement.

9. Click Start.

   The Start dialog box opens, in which you can make job settings and start the job.

4.1.3 Adding Missing Residues

Some structures are missing entire residues, even though the sequence may be complete. The residues where the break occurs are not color-coded on import into Maestro. If your structure has missing residues that could be important, you should consider doing a Prime structure prediction before proceeding with Induced Fit Docking.

To check for missing residues:

1. If the sequence viewer is not displayed in the main window, choose Sequence Viewer from the Display menu.
2. From the Color all atoms by scheme button menu on the main toolbar, choose Molecule Number.
3. Scan the sequences in the sequence viewer for changes in color.

   These changes indicate a break in the sequence.

To predict the structure of the missing residues:

1. Choose Structure Prediction from the Prime submenu of the Applications menu.

   The Prime Structure Prediction panel opens.

2. In the Input Sequence step, click From File, and import the sequence from the PDB file.

   You must import the sequence directly from the PDB, not from the Workspace, because the PDB sequence is complete and the Workspace sequence is not. Using the Workspace sequence would result in deletions.

3. Proceed to the Find Homologs step.
4. Click Import, and import the PDB file as the template.
5. Proceed with the Comparative Modeling path (see Chapter 5 of the *Prime User Manual*).

4.1.4 Geometry Adjustments

You might also have to adjust the geometry of some groups in the active site. Check particularly for GLN and ASN: the N and O atoms can look the same in the X-ray structure determination, so they might need to be flipped at their terminal dihedral if there is a poor hydrogen-bonding pattern or steric clashes. Likewise, the ring in HIS might need to be flipped. You can do this by rotating the dihedral angle by 180°.

To rotate a dihedral angle:

1. Choose Dihedral from the Adjust distances, angles, or dihedrals button menu on the main toolbar.

2. Pick four atoms that define the dihedral.

   The fourth atom should be one of the atoms in the group you want to flip. Markers and the value of the angle are displayed.

3. Drag horizontally with the middle mouse button until the angle has changed by 180°.

4.1.5 Adjusting Protonation and Tautomerization

Check for the correct protonation and tautomerization of HIS residues, and for protonation of ASP, GLU, LYS, and ARG. Check for occurrences of two basic or two acidic groups that are close to each other: one of the side chains may be better modeled as the neutral form.

To protonate a neutral atom:

1. Change the formal charge on the atom to the correct value.
2. From the Add hydrogens button menu on the main toolbar, choose Atoms.

3. Click on the atom that you want to protonate.
4. Check that the formal charge is now correct by labeling the atoms, as described above.

To deprotonate an atom:

1. From the Delete button menu on the main toolbar, choose Atoms.

2. Click on the hydrogen you want to remove.
3. Click the Decrement formal charge button on the Build panel toolbar.

4. Click on the atom to which the hydrogen was attached.

5. Check that the formal charge is now correct by labeling the atoms, as described above.

To change the tautomerization:

1. Delete the hydrogen atom that needs to be moved (use the Delete button menu on the main toolbar).
2. Change the bond orders between the atoms to reflect the new tautomer.
3. Change any formal charges to reflect the new tautomer.
4. Add the hydrogen to its new location (use the Add hydrogens button menu on the main toolbar).

4.1.6 Testing the Structure

To test the structure, it is a good idea to run a Prime energy calculation. If the Prime energy does not look reasonable, it is likely that some problems have not been fixed. You should then inspect the protein for possible remaining problems.

To run a Prime energy calculation:

1. From the Prime submenu of the Applications menu, choose Refinement.

   The Prime Refinement panel opens.
2. From the Task option menu, choose Calculate Energy.
3. Click Start.

   The Start dialog box opens.
4. Make any job settings, then click Start.

4.2 Preparation of the Ligands To Be Docked

Each ligand that will be docked to the receptor must also meet certain requirements. Like the receptor, it must have correct bond orders, formal charges, and a complete set of hydrogens for a valid ionization state. You can run the ligands through the Schrödinger application LigPrep to produce one or more desired ligand conformations and ionization states. See the *LigPrep User Manual* for information on this application.

In addition to the structure preparation, the names of the atoms in each ligand to be docked must satisfy two conditions:

- All atoms in the ligand must have the same PDB Residue Name, Residue Number, and Chain Name. This condition is satisfied automatically during job execution, so you do not

need to do anything. The program sets the PDB residue name to "UNK ", the chain name to Z, the residue number to 999, and the insertion code to blank. These values ensure that there is no conflict with the receptor.

- All atoms must have PDB Atom Names that are unique within the ligand residue, as required for parameter generation. This condition is NOT satisfied automatically during job execution, and you must correct the ligand if it does not satisfy this condition. If it does not, you must first ensure that the ligand is a single residue.

To check whether a ligands satisfies these conditions and correct it if it does not, use the procedures below. Before doing so, ensure that only the ligand is displayed in the Workspace.

The ligands to be docked must be in a single Maestro file. If you have prepared ligands in Maestro, you should export them to a Maestro file.

To check that all atoms in the ligand residue have the same residue information:

1. From the Display menu, choose Atom Labels.

   The Atom Labels panel opens.

2. In the Composition folder, clear all selections, then select Residue name, Residue number, and Chain name.
3. Ensure that the Mode option is Add.
4. Click All in the Label Atoms section.

The labels are displayed, which you can examine to ensure that they are the same.

To correct the residue information:

1. Open the Build panel.
2. In the Residue Properties folder, choose the property from the Property option menu.
3. Enter a value in the appropriate text box.
4. Click All.

To check that all atoms have unique PDB atom names within the residue:

1. Include only the ligand in the Workspace.
2. From the Display menu, choose Atom Labels.

   The Atom Labels panel opens.

3. In the Composition folder of the Atom Labels panel, clear all selections, then select PDB atom name.

4. Ensure that the Mode option is Add.
5. Click All in the Label Atoms section.

To correct ligands that do not have unique PDB atom names:

1. Open the Build panel.
2. In the Atom Properties folder, choose PDB Atom Name from the Property option menu.
3. In the Set unique PDB atom names within residues section, click All.

Running Induced Fit Docking from Maestro

The Induced Fit Docking protocol is run from Maestro using the Induced Fit Docking panel. This panel is opened from the Applications menu, by choosing Induced Fit Docking.

Before you run Induced Fit Docking, you must prepare the protein and the ligands. Instructions for these preparation tasks are given in Chapter 4.

To run the Induced Fit Docking protocol from the command line, see Chapter 6.

The features available in the Induced Fit Docking panel are described in the following subsections. Along with each panel feature, some related details about using the protocol are discussed.

To open the panel, choose Induced Fit Docking from the Applications menu.

5.1 General Panel Layout

The Induced Fit Docking panel is divided into two parts. The upper part of the panel includes the following sections, which contain options applying to more than one step of the job:

- Job options
- Glide enclosing box
- Ligands to be docked

The lower part of the panel includes sections corresponding to steps in the induced fit docking protocol:

- Step 1: Initial Glide docking
- Step 2: Prime induced fit
- Step 3: Glide redocking

Below the option sections are four buttons:

- Start—Starts the induced fit docking job.
- Write—Generates input files that can be used with the `ifd` utility to launch induced fit docking from the command line. Does not start the job.
- Reset—Resets all the settings in the Induced Fit Docking panel to their defaults.

5.2 Global Options

In the upper section of the panel you can specify options that apply to all steps of the job.

5.2.1 Job Options

The section headed Job options includes settings for the most general aspects of the job:

- Job name—The default name is `InducedFit`. Use different names for successive jobs to avoid overwriting job files and the *jobname*_`workdir` directory.
- Host—The default is `localhost`, the machine on which Maestro is running; you can also choose a remote host from the list. If you intend to distribute subjobs over multiple CPUs, choose an appropriate multiprocessor host. Note that a master job runs on the local host, even if you selected a different host to run the calculations on.

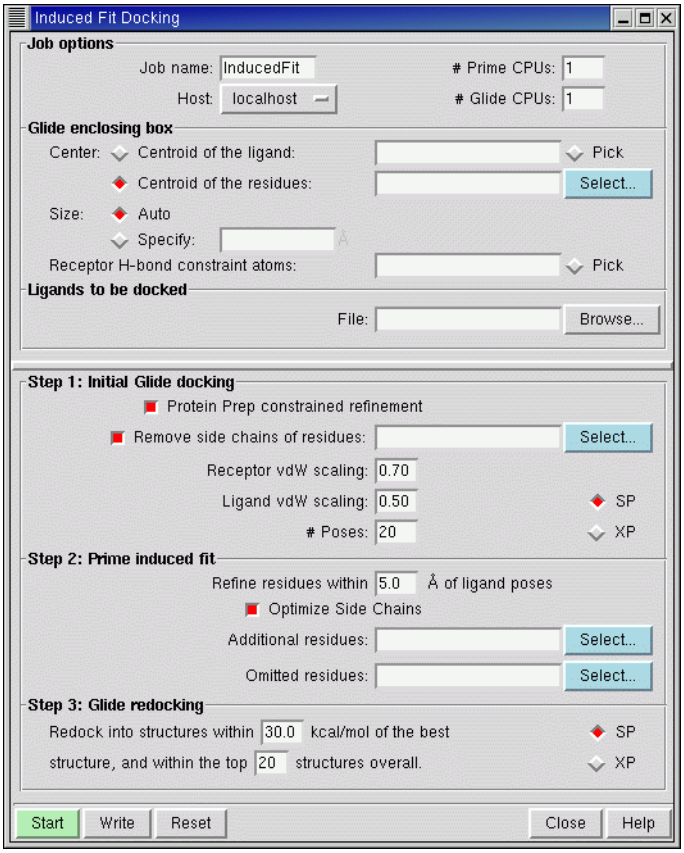

Figure 5.1. The Induced Fit Docking ***panel.***

- # Prime CPUs—The number of CPUs over which to distribute Prime subjobs. Each pose is run as a separate subjob. There is no benefit in specifying more CPUs than the number of poses.
- # Glide CPUs—The maximum number of CPUs on which to run Glide subjobs simultaneously. If multiple ligands are being docked, each can be run as a separate subjob. There is no benefit in specifying more CPUs than the number of poses.

5.2.2 Glide Enclosing Box

The section headed Glide enclosing box has options for defining the size and position of the receptor region for which grids will be generated, and also for defining H-bond constraints.

Center

- Centroid of the ligand—This option centers receptor grids at the centroid of the molecule you select as the ligand. The Select button opens the Atom Selection dialog box for ligand selection.
- Centroid of the residues—This option, which must be used if no ligand is present in the receptor structure in the Workspace, centers receptor grids at the centroid of a set of residues that you define. To choose the residues, click Select, and use the tools in the Atom Selection dialog box.

Size

- Auto—If the Center option is Centroid of the ligand, the enclosing box size is calculated automatically from the size of the ligand. If the Center option is Centroid of the residues, the enclosing box size is set to 26 Å on a side.
- Specify—Select this option to specify the length of each edge of the enclosing box.

Receptor H-bond constraint atoms

Select Pick to pick atoms in the receptor structure to be used for Glide H-bond constraints. The atoms should be hydrogen-bond acceptors (e.g. O, N, S, with lone pairs available) or hydrogen-bond donors (e.g. H in OH, NH, SH groups). The atoms that are picked are listed in the text box. Symmetry-related atoms (such as the other O atom in a carboxylate group) are automatically included as constraints, so you only need to pick one. The H-bond constraints that you define will be used as required constraints in both docking steps. The constraints are applied using the default feature sets for hydrogen-bond donors and acceptors. For more information on H-bond constraints in Glide, see Section 6.4.2 and Section 7.4.2 of the *Glide User Manual*.

5.2.3 Ligands To Be Docked

Use the Browse button to open a file selector and specify the file containing one or more ligand structures to be docked. The file name is displayed in the File text box.

5.3 Step-Specific Options

Step 1: Initial Glide docking

- Protein Prep constrained refinement—Selected by default, this option specifies that the refinement portion of the Glide Protein Preparation facility be run on the receptor. The constrained minimization ends when the RMSD is 0.18 Å or less.
- Remove side chains of residues—Select this option if you want to remove the side chains of one or more residues during initial docking. After selecting the option, click the Select button to open the Atom Selection dialog box and select the residues for which side chains should be temporarily removed. This is equivalent to mutating the selected residues to alanine for the initial docking procedure. The original residue types are retained, and used to restore the original side chains later in the Induced Fit Docking process. For more information on selecting side chains, see Section 5.4 on page 55.
- Receptor vdW scaling—By default, van der Waals radii of nonpolar receptor atoms are scaled by a factor of 0.50 for the initial Glide docking. If you have specified one or more residues for side-chain removal, the default scaling factor is automatically changed to 0.70. The binding-site residue mutation is expected to reduce the need to soften the receptor potential by vdW radii scaling.
- Ligand vdW scaling—The default scaling factor for nonpolar ligand atoms is 0.50.
- # Poses—The default maximum number of poses to keep for each ligand is 20. If you are docking many ligands, you should consider reducing the number of poses to keep.
- Precision options
  - SP—Standard-precision Glide docking. This is the default.
  - XP—Extra-precision Glide docking. Use this option only when you are docking a limited number of expected good-binding ligand conformations, such as a small set of known actives or the top-scoring 20% of ligands from a Glide SP docking job.

Step 2: Prime induced fit

- Refine residues within *n* Å of ligand poses—The default, 5.0 Å, is recommended. With smaller values, jobs will run faster but the results may not be good if significant side-chain movement is necessary to accommodate the new ligand. With larger values, jobs

will run slower but not necessarily yield better results. While 5.0 Å is the recommended value, values ranging from about 4 – 8 Å are reasonable to try.

- Optimize side chains—By default, side chains are optimized. If this option is deselected, Prime skips the optimization of side chains and proceeds with the minimization of the selected residues and ligand. Skipping the side-chain optimization results in a faster calculation. Apart from speed, you might want to deselect this option if you are confident that the side chain conformations are essentially correct, or want to relax the structure without risking putting the side chains in new, and possibly incorrect, conformations.
- Additional residues—Click the Select button to choose residues that should undergo Prime refinement even if they are more than *n* Å distant from any ligand pose. This button opens the Atom Selection dialog box.
- Omitted residues—Click the Select button to specify residues that need not undergo Prime refinement even if they are within *n* Å of a ligand pose. This button opens the Atom Selection dialog box.

For more information on selecting residues for refinement, see Section 5.5 on page 56.

Step 3: Glide redocking

- Redock into structures within *n* kcal/mol of the best structure, and within the top *m* structures overall—The default for the window *n* is 30.0 kcal/mol, and the maximum number of structures *m* defaults to 20, though of course it cannot exceed the number of ligand poses generated in the initial Glide docking step.
- Precision options
  - SP—Standard-precision Glide docking. This is the default.
  - XP—Extra-precision Glide docking. This option is recommended only when you are redocking a small number of low-energy structures. To ensure that this is the case, you can make the redocking window *n* narrower than the default, reduce the maximum number of structures *m* to be redocked, or both.

5.4 Selecting Side Chains for Removal

In the initial docking, you can remove the side chains of some residues to ensure that they do not prevent the ligands from docking in the preferred orientation. This is important if the side chains move significantly upon docking. It is also important if there is more than one binding mode, and if there were problems in the PDB structure. As a general rule-of-thumb, you should select no more than three side chains. The residues containing these side chains are temporarily mutated to alanine for the initial docking step.

The following paragraphs describe situations in which you would want to choose residues for mutation in decreasing order of importance.

a. If the protein is apo and there are existing holo proteins, superimpose the apo structure on one of the holo proteins and select residues in the active site that adopt significantly different positions.

b. If there are side chains with multiple occupancy (colored green on PDB import) or have missing density (colored red on PDB import), and either are within 5 Å of the ligand, they should be included in the side chain mutation.

c. If there are multiple structures in the unit cell (that have been independently solved in the X-ray structure determination, for example), superimpose these structures with the Protein Structure Alignment panel (Tools menu), and look at the active site residues. Any residues for which the side chains are in different locations should be considered for mutation.

d. Any side chain with a temperature factor (B) greater than about 40 should be considered for mutation, but not if the whole structure has high B values. If the whole structure has high temperature factors, then rank the residues in order of decreasing temperature factors and chose from the top of this list until a maximum of 3 residues is chosen.

5.5 Selecting Residues for Refinement

In general, you should choose residues for refinement that are within 5 Å of the active site, which is the default. To these you should add residues beyond this limit that have large motion—for example, if they are part of a helix or loop that goes close to the active site.

It is usually not necessary to omit residues. If you are confident that the side chains are fixed, such as if they are bound to a metal ion, you could omit the refinement of these residues. In the case that there is a metal ion in the active site, the protein side chains that are ligating the metal should be omitted.

5.6 Induced Fit Docking Results

When an Induced Fit Docking job finishes, it creates a Maestro file named *jobname*_out.mae and a project named *jobname*_results.prj in the launch directory. This file contains the output poses with their IFDScore. This score is the sum of the GlideScore from the redocking step and 5% of the Prime energy from the refinement calculation.

To view the results, you can open the project or import the structures from the Maestro file. The structures in the project are ordered by their IFDScore. By default, only the ligand and the residues that were refined are displayed in the Workspace.

Running Induced Fit Docking from the Command Line

If you simply want to run the standard Induced Fit Docking protocol, the Induced Fit Docking panel in Maestro provides the easiest means of running the calculations, with a range of options. If you want to set up options that are not available from Maestro, customize the steps in the protocol, add steps or rearrange steps, you can do so by editing the input file and submitting the job from the command line. The input file is designed so that you can tailor the protocol to your specific task, within the scope of the tools available.

6.1 The ifd Command

You can use the `ifd` command to launch an Induced Fit Docking job from the command line:

```
$SCHRODINGER/ifd [options] jobname.inp
```

The job settings, including host and number of CPUs, are taken from the input file. You must run this script in the directory in which *jobname*`.inp` resides. The command supports the standard Job Control options `-NICE` and `-WAIT`. The format of the input file is described in the next section.

6.2 The ifd Input File

The input file for the `ifd` command defines the stages of the protocol and the order in which they are executed in addition to defining the input settings for each stage. This means that you can define your own protocol with the available stages. You can specify any stage multiple times, and the stages are run in the order in which you specify them.

The input file is structured as follows:

```
<Global Settings section>
STAGE stage-name1
  <Stage settings>
STAGE stage-name2
  <Stage settings>
...
```

Each group of settings consists of a line containing a keyword and its value. The settings for a stage apply only to that stage. If you repeat a stage, the settings revert to their defaults unless you explicitly set them. The list of stages is given in Table 6.1.

Table 6.1. Description of stages in the induced fit docking protocol.

Stage	Description
COMPILE_RESIDUE_LIST	Compile a list of residues for refinement.
GLIDE_DOCKING	Dock ligands using Glide. This stage includes both grid generation and ligand docking.
PPREP	Prepare the protein using the refinement part of the Glide protein preparation facility.
PRIME_LOOP	Perform a Prime loop prediction for the specified loop.
PRIME_MINIMIZATION	Perform a Prime minimization on the compiled list of residues.
PRIME_REFINEMENT	Perform a Prime refinement on the compiled list of residues.
SCORING	Calculate scores for the poses.
SORT_AND_FILTER	Sort and filter poses.
TRIM_SIDECHAINS	Temporarily mutate the specified residues to alanine, to remove side chains for a following docking stage.

Some keywords take a residue, a list of residues, or a list of atoms as their value. Residues are specified in the format *chain*:*residue*, where *chain* is the single-letter chain name and *residue* is the residue number and insertion code, for example `A:151C`. Atoms are specified in the format *chain*:*residue*:*atom*, where *atom* is the PDB atom name, for example `A:151:_N__`, and underscores are used instead of blanks. In the descriptions below, *residue-spec* and *atom-spec* are used to denote these specifications.

6.2.1 Global Settings

This section contains settings that affect the whole job, and consists of host settings and receptor input file definitions. The keywords for this section are given in Table 6.2. Note that there is no benefit in specifying more CPUs than the number of poses.

6.2.2 The PPREP Stage

The `PPREP` stage has one setting, `RMSD` *value*, which specifies the convergence threshold for the constrained minimization of the Glide protein preparation. The minimization ends when the RMSD is less than or equal to *value*.

Table 6.2. Keywords for the global settings section

Keyword	Description
INPUT_FILE	Specify the file name for the receptor. Multiple receptors can be specified, either in a single file or by including multiple instances of this keyword.
NUM_GLIDE_CPUS	The maximum number of CPUs over which to distribute Glide subjobs. When docking multiple ligands, each can be run as a separate subjob. Default: 1.
NUM_PRIME_CPUS	Specify the number of CPUs over which to distribute Prime subjobs. Each pose is run as a separate subjob. Default: 1.
SUBJOB_HOST	Specify the host on which to run Glide and Prime subjobs. Default is `localhost`.

6.2.3 The TRIM_SIDECHAINS Stage

This stage has a single keyword, `RESIDUES`, which is followed by a list of residue specifications. The list specifies the residues whose side chains should be temporarily removed by mutating the residues to alanine. The next Glide docking step uses the mutated residues. The original residue types are retained, and used to restore the original side chains later in the Induced Fit Docking process. For more information on selecting side chains, see Section 5.4 on page 55.

6.2.4 The GLIDE_DOCKING Stage

This stage performs the Glide grid generation and ligand docking. Settings for Glide are made in this section. If multiple receptors are specified in the input files, the settings that define the number of poses are applied to each receptor.

Table 6.3. Keywords for the GLIDE_DOCKING stage.

Keyword	Description
BINDING_SITE	Grid center. The center can be specified in one of the following ways: `coords` *x*,*y*,*z* `ligand` *residue-spec* `residues` *residue-spec*, *residue-spec*, ... `coords` specifies the grid center directly; `ligand` specifies the centroid of the ligand, and `residues` specifies the centroid of the listed residues.
CONSTRAINT_ATOMS	Comma-separated list of Glide H-bond constraint atoms: *atom-spec*, *atom-spec*, ... Any constraints that are set are applied in docking: there are no optional constraints.
CV_CUTOFF	Threshold for rejecting poses based on Coulomb-van der Waals energy. Poses are rejected if the energy is greater than the threshold. Default: 0.00

Table 6.3. Keywords for the GLIDE_DOCKING stage.

Keyword	Description
HBOND_CUTOFF	Threshold for rejecting poses based on hydrogen bonding energy. Poses are rejected if the energy is greater than the threshold. Default: 0.00
INNER_BOX	Dimension of ligand bounding box. Default: 10.0
LIGAND_CCUT	Partial charge threshold for scaling ligand van der Waals radii. Default: 0.15
LIGAND_FILE	Name of ligand file. Must be in Maestro format. No default.
LIGAND_SCALE	Scaling factor for ligand van der Waals radii. Default: 0.80
LIGANDS_TO_DOCK	List of ligands to dock from the ligand file. Can take the values all, self (ligand that was last docked with this receptor),or a comma-separated list of integers with no white space. Default: all
MAX_LIG_ATOMS	Maximum number of ligand atoms. Ligands that do not meet this criterion are discarded. Default: 200
MAX_POSESPERLIG	Maximum number of poses per ligand. Default: 1
MAX_ROT_BONDS	Maximum number of rotatable bonds. Ligands that do not meet this criterion are discarded. Default: 35
MAX_TOTALPOSES	Maximum total number of poses. Default: 1000
MINIMUM_POSES	Redock without H-bond filtering if less than this number of poses is found. Default: 0
OUTER_BOX	Dimension of grid enclosing box. Can take the value auto or a number. The value auto computes the box size from the size of the ligand, if the grid is centered on the ligand, or sets it to 26 Å if the grid is centered on the centroid of a set of residues. Default: auto
PRECISION	Glide docking precision. Can take the values SP or XP. Default: SP
RECEPTOR_CCUT	Partial charge threshold for scaling receptor van der Waals radii. Default: 0.25
RECEPTOR_SCALE	Scaling factor for recptor van der Waals radii. Default: 1.00

6.2.5 The COMPILE_RESIDUE_LIST Stage

The list of residues for Prime refinement is compiled in this section. The initial list includes all residues within a prescribed distance of the ligand (whose identity can be specified in terms of a set of residues). To this list specified residues that lie outside this cutoff can be added, and specified residues inside the cutoff can be omitted.

Table 6.4. Keywords for the COMPILE_RESIDUE_LIST stage.

Keyword	Description
CENTER	List of residues from which to measure the cutoff distance. Default: Z:999, which is the default for the ligand.
DISTANCE_CUTOFF	Cutoff distance (in angstroms) from the ligand pose, within which residues that have any atoms are included in the refinement list. Default: 5.0
RESIDUES_TO_ADD	Comma-separated list of residues to add to the refinement list. These should be residues that lie outside the distance cutoff
RESIDUES_TO_OMIT	Comma-separated list of residues to omit from the refinement list.

6.2.6 The PRIME_REFINEMENT and PRIME_MINIMIZATION Stages

These stage perform a Prime refinement or a Prime minimization: In Prime refinement, the side chains of the residue list compiled previously are optimized, then the residues are minimized along with the ligand. There is only one setting: NUMBER_OF_PASSES *n*. By default, only one pass through Prime refinement is performed, which consists of three steps:

1. Optimize side chains.
2. Minimize residues.
3. Minimize residues and ligand.

If multiple passes are requested, the first two steps are executed the number of times specified specified by *n*. Multiple passes could be useful if, for example, the active site is extremely packed. The minimization would open up the structure somewhat and allow a better side-chain prediction.

In Prime minimization, only the last two steps are performed, and they are performed only once. There are no settings for PRIME_MINIMIZATION. A Prime minimization is faster than a Prime refinement. You might want to use a Prime minimization if you are confident that the side chain conformations are essentially correct, or want to relax the structure without risking putting the side chains in new, and possibly bad, conformations.

6.2.7 The PRIME_LOOP Stage

This stage performs a Prime loop prediction. If the receptor has a particularly flexible loop that might preclude ligand binding even with a softened potential, you could consider doing a loop prediction before the initial Glide docking. If there are more subtle loop movements associated with ligand binding that cannot be reached by minimization alone, you could consider adding a loop prediction after the Prime refinement.

Table 6.5. Keywords for the PRIME_LOOP stage

Keyword	Description
START_RESIDUE	First residue in the loop.
END_RESIDUE	Last residue in the loop.
DISTANCE_CUTOFF	Threshold for inclusion of residues for side-chain refinement. Any residues with atoms within this distance are included. Default: 5.0
MAX_ENERGY_GAP	Energy threshold for predicted loop structures (in kcal/mol). Structures are discarded if their energy is more than this amount above the lowest-energy structure. Default: 10000.0
MAX_STRUCTURES	Maximum number of structures to retain. Default: 1000
INCLUDE_RESIDUE_LIST	Include the residues from COMPILE_RESIDUE_LIST for side-chain refinement. Can take values TRUE or FALSE. Default: FALSE

In addition to predicting the loop itself, you can refine the side chains of other residues along with the loop. These residues can be selected beforehand with a COMPILE_RESIDUE_LIST stage, and added by setting INCLUDE_RESIDUE_LIST to TRUE, or added as a shell of residues within a distance specified by DISTANCE_CUTOFF. If you specify extra residues by both mechanisms, all members of both sets are included.

6.2.8 The SORT_AND_FILTER Stage

The sorting and filtering stage first groups all structures by the ligand contained within each structure. The poses for a particular ligand are then sorted by the property specified by POSE_FILTER. POSE_KEEP can then be used to keep the best poses, defined as those that have the smallest (most negative) value of the property, and discard the rest. After this filtering step, the groups of poses for each ligand are sorted by the property specified by LIGAND_FILTER for the top pose in each group. LIGAND_KEEP can then be used to discard entire ligand groups, in the same way as with POSE_KEEP.

6.2.9 SCORING Settings

In this stage you can define the scoring function in terms of Maestro properties that are available in the output file from each stage. The defaut scoring function when you run Induced Fit Docking from Maestro is a two-term function that adds 0.05 of the Prime energy to the GlideScore. You can provide a name for the property, which is written to the output Maestro file and can be displayed in the Project Table.

To define the scoring function, include TERM settings for each property that you want to include in the scoring function. The property must come from the Maestro output file of one of

Table 6.6. Keywords for the SORT_AND_FILTER stage.

Keyword	Description
POSE_FILTER	Name of Maestro property for filtering poses, for example, r_psp_Prime_Energy
POSE_KEEP	Threshold on property for filtering poses. The syntax is as follows: *n*% Keep the *n*% of poses with the lowest property values *n*# Keep the *n* poses with the lowest property values *n* Keep poses with property values within *n* of the lowest value.
LIGAND_FILTER	Name of Maestro property for filtering ligands, for example, r_psp_Prime_Energy
LIGAND_KEEP	Threshold on property for filtering ligands. The syntax is the same as for POSE_KEEP.

the previous stages. For the purpose of generating a scoring function, the stages are indexed by counting stages that produce output files backwards from the current stage, starting from zero. As an example, the indexes of the stages are shown to the left for the following sequence of stages.

```
4    STAGE PPREP
3    STAGE PRIME_LOOP
2    STAGE GLIDE_DOCKING
     STAGE COMPILE_RESIDUE_LIST
1    STAGE PRIME_REFINEMENT
     STAGE SORT_AND_FILTER
     STAGE SORT_AND_FILTER
0    STAGE GLIDE_DOCKING
     STAGE SCORING
```

Table 6.7. Keywords for the global settings section

Keyword	Description
SCORE_NAME	Name of property to add to Maestro files. Must bein the format r_psp_*name*, where *name* is the property name displayed in Maestro.
TERM	Add a term to the scoring function. You can include multiple TERM keywords to define the scoring fuction. Format: *coeff , property , stage,* where *coeff* is the coefficient, *property* is the property from the Maestro output file, and *stage* is the index of the property-generating stage, counting backwards in the input file with 0 for the previous stage.
REPORT_FILE	CSV file containing ligand number, score, score terms, and file name of the structure. Default: scores.csv

The stages that do not generate a Maestro output file are COMPILE_RESIDUE_LIST, SORT_AND_FILTER, and SCORING. The SCORING stage adds the score to the Maestro file from the last stage.

The output from the scoring stage is a comma-separated value (CSV) file containing (in order) the ligand number, (which is always 1), the score, the list of terms in the score, and the filename for the structure. The rows are sorted by the score. The CSV file and the files for the structures are in the *jobname*_workdir subdirectory. The default name is scores.csv.

6.2.10 Sample Input File

A sample input file, showing the default values, is given below. This file was generated for the tutorial example by clicking Write in the Induced Fit Docking panel. The comments are generated when the file is written.

```
# Global Variables
#  These variables affect the entire job, and must all appear
#  before the first STAGE declaration.  Multiple INPUT_FILE
#  entries are supported, as are files containing multiple
#  receptor structures.
INPUT_FILEInducedFit1_rec.mae
SUBJOB_HOSTlocalhost
NUM_PRIME_CPUS1
NUM_GLIDE_CPUS1

# Protein Preparation
#  Run a simple constrained minimization of the receptor
#  structure(s).
STAGE PPREP
  RMSD0.18

STAGE TRIM_SIDECHAINS
  RESIDUESA:10B
# Prime Loop Prediction
#  Perform a loop prediction on the specified loop, including
#  side chains within the given distance.  Only return
#  structures within the specified energy range from the
#  lowest energy prediction, up to the maximum number of
#  conformations given.
#
#  Note: This stage is disabled by default.  Uncomment the
#   lines below and edit the fields appropriately to enable it.
#STAGE PRIME_LOOP
#  START_RESIDUE A:11
#  END_RESIDUE A:16
#  DISTANCE_CUTOFF 5.0
#  MAX_ENERGY_GAP 30.0
```

```
#  MAX_STRUCTURES 5

# Glide Docking
#  Perform the initial Glide docking, producing a
#  ligand-receptor complex for each pose requested/found.
#  If multiple receptor structures are used, the requested
#  number of poses will be generated for each structure.
STAGE GLIDE_DOCKING
  RECEPTOR_CCUT0.25
  LIGAND_FILEInducedFit1_lig.mae
  LIGANDS_TO_DOCKall
  LIGAND_CCUT0.15
  CV_CUTOFF100.0
  HBOND_CUTOFF-0.05
  INNER_BOX10.0
  BINDING_SITEligand _:400
  OUTER_BOXauto
  RECEPTOR_SCALE0.70
  LIGAND_SCALE0.50
  MAX_POSESPERLIG 2
  PRECISIONSP

# Determine Residue to Refine
#  Compile a list of all residues within the specified
#  distance of any pose of the ligand.
STAGE COMPILE_RESIDUE_LIST
  DISTANCE_CUTOFF3.4

# Prime Refinement
#  Optimize the side chains of the residue list compiled
#  previously, then minimize them along with the ligand.
STAGE PRIME_REFINEMENT
  NUMBER_OF_PASSES1

# Sort and Filter
#  Only retain poses with Prime Energies within the
#  specified range from the lowest energy pose.
STAGE SORT_AND_FILTER
  POSE_FILTERr_psp_Prime_Energy
  POSE_KEEP30.0

# Sort and Filter
#  Only retain the top number of poses specified.
STAGE SORT_AND_FILTER
  POSE_FILTERr_psp_Prime_Energy
  POSE_KEEP20#

# Glide Docking
#  Redock the ligand back into the newly optimized receptor,
```

```
#  using default Glide settings.
STAGE GLIDE_DOCKING
  BINDING_SITEligand Z:999
  RECEPTOR_SCALE1.00
  RECEPTOR_CCUT0.25
  LIGAND_FILEInducedFit1_lig.mae
  LIGANDS_TO_DOCKself
  LIGAND_SCALE0.80
  LIGAND_CCUT0.15
  CV_CUTOFF0.0
  HBOND_CUTOFF0.0
  MAX_POSESPERLIG1
  OUTER_BOXauto
  PRECISIONSP

# Scoring
#  Compile the IFD Score, consisting of the GlideScore for
#  the Glide Redocking plus 5% of the Prime Energy from the
#  Prime Refinement.
STAGE SCORING
  SCORE_NAME  r_psp_IFDScore
  TERM 1.0,r_i_glide_gscore,0
  TERM 0.05,r_psp_Prime_Energy,1
  REPORT_FILE report.csv
```

6.3 Files Produced

As the induced fit docking job proceeds, input files and results files are written to the *jobname*_workdir subdirectory of the output directory. Each stage in the protocol appends a descriptive suffix to the names of the files that pass through it, so that final files can have long file names. When the job finishes, the *jobname*_workdir directory contains many files. The final Maestro output file is copied to the launch directory with the name *jobname*-out.mae, and a project named *jobname*_results.prj is also created in the launch directory. The score is present as a Maestro property in these files. The scoring stage generates a comma-separated-values file in the *jobname*_workdir directory, named report.csv by default.

The files produced by an Induced Fit Docking run in the output directory are listed in Table 6.8.

Table 6.8. FIles produced by Induced Fit Docking run.

File	Description
jobname.inp	Input file, as described in Section 6.2 on page 57.
*jobname*_lig.mae	Ligands file.
jobname.log	Log file, containing details of settings for each stage and execution of stages.
jobname-out.mae	Maestro file containing the results.
*jobname*_rec.mae	Receptor file.

A sample log file, for the tutorial Induced Fit Docking run, is shown below.

```
Monitoring job: InducedFit1

TCL_LIBRARY: /zone2/NB_r2005-1/latest/python-v30106/lib/Linux-x86/tcl8.3
TK_LIBRARY: /zone2/NB_r2005-1/latest/python-v30106/lib/Linux-x86/tk8.3

==================================
  Induced Fit Docking Calculation
==================================

Started at: Sat Oct 22 11:29:27 2005
Job ID: elham-0-435a8501

Here are the parameters that will be used:

    General:
        JobHost: localhost
        #Prime CPUs: 1
        #Glide CPUs: 1
        Working Dir: /zone1/dyall/inducedfit/InducedFit1_workdir

    Stage: Protein Preparation
        Max RMSD:   0.18

    Stage: Trimming Sidechains
        Residues:     A:10B

    Stage: Glide Docking
        Receptor Scaling:        0.70
        Receptor Scaling Cutoff: 0.25
        Ligand Source:           InducedFit1_lig.mae
        Ligand To Dock:          all
        Precision:               SP
        Ligand Scaling:          0.50
        Ligand Scaling Cutoff:   0.15
        CV Cutoff:               100.0
```

```
        H-Bond Cutoff:           -0.05
        Poses Per Ligand:        2
        Minimum Poses:           0

    Stage: Determine Residues for Refinement
        Distance Cutoff: 3.4 A
        Additional Residues:
        Omit Residues:

    Stage: Prime Active Site Optimization
        Number of Passes: 1

    Stage: Sorting and Filtering
        Pose Filter:     r_psp_Prime_Energy
            Keep:        30.0
        Ligand Filter:   <none>
            Keep:        <none>

    Stage: Sorting and Filtering
        Pose Filter:     r_psp_Prime_Energy
            Keep:        20#
        Ligand Filter:   <none>
            Keep:        <none>

    Stage: Glide Docking
        Receptor Scaling:        1.00
        Receptor Scaling Cutoff: 0.25
        Ligand Source:           InducedFit1_lig.mae
        Ligand To Dock:          self
        Precision:               SP
        Ligand Scaling:          0.80
        Ligand Scaling Cutoff:   0.15
        CV Cutoff:               0.0
        H-Bond Cutoff:           0.0
        Poses Per Ligand:        1
        Minimum Poses:           0

    Stage: Scoring
        Score =   + 1.0 r_i_glide_gscore(0)  + 0.05 r_psp_Prime_Energy(1)
        Report File: report.csv

Number of initial structures: 1

Stage: Protein Preparation
    Job elham-0-435a850a launched.
    Job elham-0-435a850a finished.
    Structures to be carried forward: 1
Stage completed.  Elapsed time: 152.1 seconds
```

```
Stage: Trimming Sidechains
    Structures to be carried forward: 1
Stage completed.  Elapsed time: 0.8 seconds

Stage: Glide Docking
    Job elham-0-435a85a2 launched.
    Job elham-0-435a85a2 finished.
    Structures to be carried forward: 2
Stage completed.  Elapsed time: 213.0 seconds

Stage: Determine Residues for Refinement
    Calculating residue distances...
    Structures to be carried forward: 2
Stage completed.  Elapsed time: 9.6 seconds

Stage: Prime Active Site Optimization
    Job elham-0-435a8681 launched.
    Job elham-0-435a8681 finished.
    Job elham-0-435a87e1 launched.
    Job elham-0-435a87e1 finished.
    Structures to be carried forward: 2
Stage completed.  Elapsed time: 734.6 seconds

Stage: Sorting and Filtering
    Structures to be carried forward: 2
Stage completed.  Elapsed time: 1.6 seconds

Stage: Sorting and Filtering
    Structures to be carried forward: 2
Stage completed.  Elapsed time: 0.7 seconds

Stage: Glide Docking
    Job elham-0-435a8962 launched.
    Job elham-0-435a8962 finished.
    Job elham-0-435a8a49 launched.
    Job elham-0-435a8a49 finished.
    Structures to be carried forward: 2
Stage completed.  Elapsed time: 484.9 seconds

Stage: Scoring
    Structures to be carried forward: 2
Stage completed.  Elapsed time: 2.8 seconds

Completed at: Sat Oct 22 11:56:12 2005
Total elapsed time: 1603.8 seconds
```

Getting Help

Schrödinger software is distributed with documentation in PDF format. If the documentation is not installed in `$SCHRODINGER/docs` on a computer that you have access to, you should install it or ask your system administrator to install it.

For help installing and setting up licenses for Schrödinger software and installing documentation, see the *Installation Guide*.

Maestro has automatic, context-sensitive help (Auto-Help and Balloon Help, or tooltips), and an online help system. To get help, follow the steps below.

- Check the Auto-Help text box, which is located at the foot of the main window. If help is available for the task you are performing, it is automatically displayed there. Auto-Help contains a single line of information. For more detailed information, use the online help.
- If you want information about a GUI element, such as a button or option, there may be Balloon Help for the item. Pause the cursor over the element. If the Balloon Help does not appear, check that Show Balloon Help is selected in the Help menu of the main window. If there is Balloon Help for the element, it appears within a few seconds.
- For information about a panel or the folder that is displayed in a panel, click the Help button in the panel. The Help panel is opened and a relevant help topic is displayed.
- For other information in the online help, open the Help panel and locate the topic by searching or by category. You can open the Help panel by choosing Help from the Help menu on the main menu bar or by pressing CTRL+H.

If you do not find the information you need in the Maestro help system, check the following sources:

- *Glide User Manual*, for information on using Glide
- *Glide Quick Start Guide*, for Glide tutorials
- *Prime User Manual*, for information on using Prime
- *Prime Quick Start Guide*, for Prime tutorials
- *Maestro User Manual*, for detailed information on using Maestro
- *Maestro Tutorial*, for a tutorial on the basic features of Maestro
- Frequently Asked Questions pages, at https://www.schrodinger.com/InducedFit_FAQ.html

The manuals are also available in PDF format from the the Schrödinger Support Center. Information on additions and corrections to the manuals is available from this web page.

If you have questions that are not answered from any of the above sources, contact Schrödinger using the information below.

E-mail: help@schrodinger.com
USPS: 101 SW Main Street, Suite 1300, Portland, OR 97204
Phone: (503) 299-1150
Fax: (503) 299-4532
WWW: http://www.schrodinger.com
FTP: ftp://ftp.schrodinger.com

Generally, e-mail correspondence is best because you can send machine output, if necessary. When sending e-mail messages, please include the following information, most of which can be obtained by entering `$SCHRODINGER/machid` at a command prompt:

- All relevant user input and machine output
- Glide/Prime purchaser (company, research institution, or individual)
- Primary Glide/Prime user
- Computer platform type
- Operating system with version number
- Prime version number
- Glide version number
- Maestro version number
- mmshare version number

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